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- (S7) Abstract:** The present invention provides compositions and methods relating to or derived from anti-IGF-1R antibodies. In particular embodiments, the invention provides fully human, humanized, or chimeric antiIGF-1R antibodies that bind human IGF-1R, IGF-1R-binding fragments and derivatives of such antibodies, and IGF-1R-binding polypeptides comprising such fragments. Other embodiments provide nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating or diagnosing subjects having IGF-1R-related disorders or conditions.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**COMPOSITIONS AND METHODS RELATING TO ANTI-IGF-1 RECEPTOR ANTIBODIES****5 REFERENCE TO RELATED APPLICATION**

This application claims the benefit of U.S. Provisional Application Ser. No. 60/638,961, filed on December 22, 2004, and is incorporated by reference herein.

**10 FIELD OF THE INVENTION**

This application provides compositions and methods relating to anti-IGF-1 receptor antibodies.

**BACKGROUND OF THE INVENTION**

15 Insulin-like growth factors 1 and 2 (IGF-1 and IGF-2, respectively) promote the differentiation and proliferation of a wide variety of mammalian cell types.

IGF-1 and IGF-2 both circulate widely throughout the body in plasma. They exert their effects on cells by binding to and activating the IGF-1 receptor (IGF-1R). IGF-1R is a member of the family of tyrosine kinase growth factor receptors. Its amino acid sequence is about 70% identical to that of the insulin receptor.

20 Abnormal IGF-1, IGF-2, and/or IGF-1R activities are associated with a number of medical conditions, including various types of cancer, growth defects (*e.g.*, acromegaly, gigantism, and small stature), psoriasis, atherosclerosis, post angioplasty smooth muscle restonsis of blood vessels, diabetes, microvascular proliferation, neuropathy, loss of muscle mass, and osteoporosis.

**25 BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 provides nucleotide sequences encoding light chain variable domains L1 through L52 and heavy chain variable domains H1 through H52.

Figure 2 provides amino acid sequences of light chain variable domains L1 through L52. CDR and FR regions are indicated.

30 Figure 3 provides amino acid sequences of heavy chain variable domains H1 through H52. CDR and FR regions are indicated.

Figure 4 provides amino acid sequences of the light chain CDR1 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

35 Figure 5 provides amino acid sequences of the light chain CDR2 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 6 provides amino acid sequences of the light chain CDR3 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 7 provides amino acid sequences of the heavy chain CDR1 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

40 Figure 8 provides amino acid sequences of the heavy chain CDR2 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 9 provides amino acid sequences of the heavy chain CDR3 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 10 provides the amino acid sequence of a human IGF-1R extracellular domain fused to a human IgG1 Fc region (underlined) with an intervening caspase-3 cleavage site (**bold**).

5 Figure 11 provides the amino acid sequence of a human insulin receptor extracellular domain fused to a human IgG1 Fc region (underlined).

Figure 12 provides the protein sequence of a human IGF-1R extracellular domain (including signal peptide) fused at the C-terminus with chicken avidin. The initiating met in the IGF-1R ECD is designated position 1 in this figure.

10 Figure 13 provides the polypeptide sequence of a human kappa light chain antibody constant region and a human IgG1 heavy chain antibody constant region.

Figure 14 provides a graph illustrating that four phage-displayed antibodies bind significantly better to an IGF-1R-Fc molecule than they bind to an insulin-receptor-Fc or a murine Fc.

Figure 15 provides graphs illustrating the ability of certain antibodies to compete for binding to 15 IGF-1R with IGF-1 and IGF-2.

Figure 16 provides graphs illustrating the ability of certain antibodies to inhibit the growth of 32D hu IGF-1R+IRS-1 cells.

Figure 17 provides graphs illustrating the ability of certain antibodies to inhibit the growth of Balb/C 3T3 hu IGF-1R cells.

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## SUMMARY OF THE INVENTION

In one aspect, the present invention provides an isolated antigen binding protein comprising either:

a. a light chain CDR3 comprising a sequence selected from the group consisting of: i. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions 25 from a CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L52 as shown in Figure 6; ii. M X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> X<sub>4</sub> X<sub>5</sub> P X<sub>6</sub> X<sub>7</sub>; iii. Q Q X<sub>8</sub> X<sub>9</sub> X<sub>10</sub> X<sub>11</sub> P X<sub>12</sub> T; and iv. Q S Y X<sub>13</sub> X<sub>14</sub> X<sub>15</sub> N X<sub>16</sub> X<sub>17</sub> X<sub>18</sub>; b. a heavy chain CDR3 comprising a sequence selected from the group consisting of: i. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the heavy chain 30 CDR3 sequences of H1-H52 as shown in Figure 9; ii. X<sub>19</sub> X<sub>20</sub> X<sub>21</sub> X<sub>22</sub> X<sub>23</sub> X<sub>24</sub> X<sub>25</sub> X<sub>26</sub> X<sub>27</sub> F D I; iii. X<sub>28</sub> X<sub>29</sub> X<sub>30</sub> X<sub>31</sub> X<sub>32</sub> X<sub>33</sub> X<sub>34</sub> X<sub>35</sub> X<sub>36</sub> X<sub>37</sub> X<sub>38</sub> M D V; iv. D S S X<sub>39</sub>; or c. the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b); wherein X<sub>1</sub> is a glutamine residue or a glutamate residue, X<sub>2</sub> is an alanine residue, a glycine residue, a threonine residue, or a serine residue, X<sub>3</sub> is a leucine residue, a phenylalanine residue, or a threonine residue, X<sub>4</sub> is glutamine residue, a glutamate residue, or a histidine 35 residue, X<sub>5</sub> is a threonine residue, a methionine residue, a tryptophan residue, or a valine residue, X<sub>6</sub> is a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue, X<sub>7</sub> is threonine residue, an alanine residue, or a serine residue, X<sub>8</sub> is an arginine residue, a serine residue, a leucine residue, or an alanine residue, X<sub>9</sub> is an asparagine residue, a serine residue, or a histidine residue, 40 X<sub>10</sub> is an asparagine residue or a serine residue, X<sub>11</sub> is a tryptophan residue, a valine residue, a tyrosine



residue, a proline residue, or a phenylalanine residue, X<sub>12</sub> is a leucine residue, a tyrosine residue, or an isoleucine residue, X<sub>13</sub> is an aspartate residue or a glutamine residue, X<sub>14</sub> is a serine residue or a proline residue, X<sub>15</sub> is a serine residue, a tyrosine residue, an aspartate residue, or an alanine residue, X<sub>16</sub> is a glutamine residue, an arginine residue, a valine residue, or a tryptophan residue, X<sub>17</sub> is an arginine residue, a valine residue, an isoleucine residue, or no residue, X<sub>18</sub> is a valine residue or no residue, X<sub>19</sub> is a glutamate residue or no residue, X<sub>20</sub> is a tyrosine residue, a glycine residue, a serine residue, or no residue, X<sub>21</sub> is a serine residue, an asparagine residue, a tryptophan residue, a glutamate residue, an aspartate residue, or no residue, X<sub>22</sub> is a serine residue, an aspartate residue, a tryptophan residue, an alanine residue, an arginine residue, a threonine residue, a glutamine residue, a leucine residue, a glutamate residue, or no residue, X<sub>23</sub> is a serine residue, a glycine residue, an asparagine residue, a threonine residue, a tryptophan residue, a valine residue, an alanine residue, or an isoleucine residue, X<sub>24</sub> is an arginine residue, a glutamine residue, a tyrosine residue, a valine residue, an alanine residue, a glycine residue, a serine residue, a phenylalanine residue, or a tryptophan residue, X<sub>25</sub> is an asparagine residue, a leucine residue, an aspartate residue, a threonine residue, a tryptophan residue, a tyrosine residue, a valine residue, an alanine residue, or a histidine residue, X<sub>26</sub> is an aspartate residue, a serine residue, an asparagine residue, or a glutamine residue, X<sub>27</sub> is an alanine residue or a proline residue, X<sub>28</sub> is an alanine residue or no residue, X<sub>29</sub> is a glutamate residue, a tyrosine residue, a glycine residue, or no residue, X<sub>30</sub> is an arginine residue, a serine residue, or no residue, X<sub>31</sub> is a glycine residue, an aspartate residue, a valine residue, a serine residue, or no residue, X<sub>32</sub> is a serine residue, an aspartate residue, a glycine residue, or no residue, X<sub>33</sub> is a phenylalanine residue, an aspartate residue, a tyrosine residue, a glycine residue, a serine residue, a histidine residue, a tryptophan residue, or no residue, X<sub>34</sub> is a tryptophan residue, an aspartate residue, a tyrosine residue, a serine residue, or no residue, X<sub>35</sub> is an aspartate residue, a glutamate residue, an arginine residue, a serine residue, a glycine residue, a tyrosine residue, or a tryptophan residue, X<sub>36</sub> is a tyrosine residue, a lysine residue, an isoleucine residue, a leucine residue or a phenylalanine residue, X<sub>37</sub> is a tyrosine residue, a serine residue, a phenylalanine residue, an aspartate residue, or a glycine residue, X<sub>38</sub> is a glycine residue, an asparagine residue, or a tyrosine residue, X<sub>39</sub> is a valine residue, a glycine residue, or a serine residue, and said antigen binding protein binds specifically to human IGF-1R. In one embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1

sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR3 sequence of L1-L52 as shown in Figure 6; c. a heavy chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and d. a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a heavy chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of H1-H52 as shown in Figure 8; and c. a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of L1-L52 as shown in Figure 4; and b. a heavy chain CDR2 sequence of H1-H52 as shown in Figure 8. In another embodiment, the isolated antigen binding protein comprises a CDR1 sequence of L1-L52 as shown in Figure 4. In another embodiment, the isolated antigen binding protein comprises a sequence selected from the group consisting of: a. a light chain CDR1 sequence selected from the group consisting of: i. RSSQSLHSNGYNYLD; ii. RASQ(G/S)(I/V)(G/S)X(Y/F)L(A/N); and iii. RSSQS(L/I)XXXXX; b. a

light chain CDR2 sequence selected from the group consisting of: i. LGSNRAS; ii. AASTLQS; and iii. EDNXRPS; c. a heavy chain CDR1 sequence selected from the group consisting of: i. SSNWWS; ii. XYYWS; and iii. SYAM(S/H); and d. a heavy chain CDR2 sequence selected from the group consisting of: i. (E/I)(I/V)(Y/N)(H/Y)SGST(N/Y)YNPSLKS; and ii. XIS(G/S)SG(G/S)STYYADSVKG; wherein amino acid residue symbols enclosed in parentheses identify alternative residues for the same position in a sequence, each X is independently any amino acid residue, and each Z is independently a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue. In another embodiment, the isolated antigen binding protein comprises a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises two amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises three amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises four amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six

amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises five amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain comprising: i. a light chain CDR1 sequence shown in Figure 4; ii. a light chain CDR2 sequence shown in Figure 5; and iii. a light chain CDR3 sequence shown in Figure 6; b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence shown in Figure 7; ii. a heavy chain CDR2 sequence shown in Figure 8; and iii. a heavy chain CDR3 sequence shown in Figure 9; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. light chain CDR1, CDR2, and CDR3 sequences

that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same light chain variable domain sequence selected from the group consisting of L1-L52; b. heavy chain CDR1, CDR2, and CDR3 sequences that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same heavy chain variable domain sequence selected from the group consisting of H1-H52; or c. the light chain CDR1, CDR2, and CDR3 sequences of (a) and the heavy chain CDR1, CDR2, and CDR3 sequences of (b).

In another aspect, the present invention provides an isolated antigen binding protein comprising either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 80% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1; b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 80% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein said antigen binding protein binds to human IGF-1R. In one embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 85% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 25 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1; b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 85% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 25 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c)

the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 90% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 35 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 90% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 35 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c) the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 95% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 95% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 95% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 95% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c) the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 97% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 97% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c) the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable

domain sequence selected from the group consisting of: i. a sequence of amino acids at least 99% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 99% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 99% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 99% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of L1-L52 as shown in Figure 2; b. a heavy chain variable domain sequence selected from the group consisting of H1-H52 as shown in Figure 3; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the isolated antigen binding protein further comprises: a. the kappa light chain constant sequence of Figure 13, b. the IgG1 heavy chain constant sequence of Figure 13, or c. the kappa light chain constant sequence of Figure 13 and the IgG1 heavy chain constant sequence of Figure 13. In another embodiment, the isolated antigen binding protein, when bound to IGF-1R: a. inhibits IGF-1R; b. activates IGF-1R; c. cross-competes with a reference antibody for binding to IGF-1R; d. binds to the same epitope of IGF-1R as said reference antibody; e. binds to IGF-1R with substantially the same K<sub>d</sub> as said reference antibody; or f. binds to IGF-1R with substantially the same off rate as said reference antibody; wherein said reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the isolated antigen binding protein, when bound to a human IGF-1R, inhibits binding of IGF-1 and/or IGF-2 to said human IGF-1R. In another embodiment, the isolated antigen binding protein inhibits the growth of a cancer cell by greater than about 80% in the presence of a growth stimulant selected from the group consisting of serum, IGF-1, and IGF-2. In another embodiment, said cancer cell is an MCF-7 human breast cancer cell. In another embodiment, the

isolated antigen binding protein binds to human IGF-1R with a selectivity that is at least fifty times greater than its selectivity for human insulin receptor. In another embodiment, the isolated antigen binding protein inhibits tumor growth *in vivo*. In another embodiment, the isolated antigen binding protein inhibits IGF-1R mediated tyrosine phosphorylation. In another embodiment, the isolated antigen binding protein

5 specifically binds to the IGF-1R of a non-human primate, a cynomolgous monkey, a chimpanzee, a non-primate mammal, a rodent, a mouse, a rat, a hamster, a guinea pig, a cat, or a dog. In another embodiment, the isolated antigen binding protein comprises: a. a human antibody; b. a humanized antibody; c. a chimeric antibody; d. a monoclonal antibody; e. a polyclonal antibody; f. a recombinant antibody; g. an antigen-binding antibody fragment; h. a single chain antibody; i. a diabody; j. a triabody; k. a tetraabody; l.

10 a Fab fragment; m. a F(ab')<sub>2</sub> fragment; n. a domain antibody; o. an IgD antibody; p. an IgE antibody; q. an IgM antibody; r. an IgG1 antibody; s. an IgG2 antibody; t. an IgG3 antibody; u. an IgG4 antibody; or v. an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

In another aspect, the present invention provides an isolated polynucleotide comprising a sequence

15 that encodes the light chain, the heavy chain, or both of said antigen binding protein. In one embodiment, said polynucleotide comprises a light chain variable domain nucleic acid sequence of Figure 1 and/or a heavy chain variable domain nucleic acid sequence of Figure 1. In another embodiment, a plasmid comprises said isolated polynucleotide. In another embodiment, said plasmid is an expression vector. In another embodiment, an isolated cell comprises said polynucleotide. In another embodiment, a

20 chromosome of said cell comprises said polynucleotide. In another embodiment, said cell is a hybridoma. In another embodiment, an expression vector comprises said polynucleotide. In another embodiment, said cell is a CHO cell. In another embodiment, the present invention provides a method of making an antigen binding protein that binds human IGF-1R, comprising incubating said isolated cell under conditions that allow it to express said antigen binding protein.

In another aspect, the present invention provides a pharmaceutical composition comprising the antigen binding protein. In one embodiment, the present invention provides a method of treating a condition in a subject comprising administering to said subject said pharmaceutical composition, wherein said condition is treatable by reducing the activity of IGF-1R in said subject. In another embodiment, said subject is a human being. In another embodiment, said condition is multiple myeloma, a liquid tumor, liver

30 cancer, a thymus disorder, a T-cell mediated autoimmune disease, an endocrinological disorder, ischemia, or a neurodegenerative disorder. In another embodiment, said liquid tumor is selected from the group consisting of acute lymphocytic leukemia (ALL) and chronic myelogenous leukemia (CML); wherein said liver cancer is selected from the group consisting of hepatoma, hepatocellular carcinoma, cholangiocarcinoma, angiosarcomas, hemangiosarcomas, hepatoblastoma; wherein said thymus disorder is selected from the group consisting of thymoma and thyroiditis, wherein said T-cell mediated autoimmune

35 disease is selected from the group consisting of Multiple Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE), Grave's Disease, Hashimoto's Thyroiditis, Myasthenia Gravis, Auto-Immune Thyroiditis, Bechet's Disease, wherein said endocrinological disorder is selected from the group consisting of Type II Diabetes, hyperthyroidism, hypothyroidism, thyroiditis, hyperadrenocorticism, and

40 hypoadrenocorticism; wherein said ischemia is post cardiac infarct ischemia, or wherein said



neurodegenerative disorder is Alzheimer's Disease. In another embodiment, said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an overdose of acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy. In another embodiment, the method further comprising administering to said subject a second treatment. In another embodiment, said second treatment is administered to said subject before and/or simultaneously with and/or after said pharmaceutical composition is administered to said subject. In another embodiment, said second treatment comprises radiation treatment, surgery, or a second pharmaceutical composition. In another embodiment, said second pharmaceutical composition comprises an agent selected from the group consisting of a corticosteroid, an anti-emetic, ondansetron hydrochloride, granisetron hydrochloride, metoclopramide, domperidone, haloperidol, cyclizine, lorazepam, prochlorperazine, dexamethasone, levomepromazine, tropisetron, a cancer vaccine, a GM-CSF inhibiting agent, a GM-CSF DNA vaccine, a cell-based vaccine, a dendritic cell vaccine, a recombinant viral vaccine, a heat shock protein (HSP) vaccine, an allogeneic tumor vaccine, an autologous tumor vaccine, an analgesic, ibuprofen, naproxen, choline magnesium trisalicylate, an oxycodone hydrochloride, an anti-angiogenic agent, an anti-vascular agent, bevacizumab, an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fragment, an anti-TWEAK antibody, an anti-TWEAK receptor antibody, a soluble TWEAK receptor fragment, AMG 706, AMG 386, an anti-proliferative agent, a farnesyl protein transferase inhibitor, an  $\alpha\beta 3$  inhibitor, an  $\alpha\beta 5$  inhibitor, a p53 inhibitor, a Kit receptor inhibitor, a ret receptor inhibitor, a PDGFR inhibitor, a growth hormone secretion inhibitor, an angiopoietin inhibitor, a tumor infiltrating macrophage-inhibiting agent, a c-fms inhibiting agent, an anti-c-fms antibody, an CSF-1 inhibiting agent, an anti-CSF-1 antibody, a soluble c-fms fragment, pegvisomant, gemcitabine, panitumumab, irinotecan, and SN-38. In another embodiment, said method comprises administering to said subject a third treatment. In another embodiment, said condition is a cancer, said second treatment comprises administering panitumumab, and said third treatment comprises administering gemcitabine. In another embodiment, said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an

overdose of acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy.

In another aspect, the present invention provides a method of increasing the longevity of a subject comprising administering to said subject said pharmaceutical composition.

5 In another aspect, the present invention provides a method of decreasing IGF-1R activity in a subject in need thereof comprising administering to said subject said pharmaceutical composition.

In another aspect, the present invention provides a method of decreasing IGF-1R signaling in a subject in need thereof comprising administering to said subject said pharmaceutical composition.

10 In another aspect, the present invention provides a method of inhibiting the binding of IGF-1 and/or IGF-2 to IGF-1R in a subject in need thereof comprising administering to said subject said pharmaceutical composition.

#### DETAILED DESCRIPTION OF THE INVENTION

15 The present invention provides compositions, kits, and methods relating to molecules that bind to the Insulin-Like Growth Factor Receptor ("IGF-1R"), including molecules that agonize or antagonize IGF-1R, such as anti-IGF-1R antibodies, antibody fragments, and antibody derivatives, *e.g.*, antagonistic anti-IGF-1R antibodies, antibody fragments, or antibody derivatives. Also provided are nucleic acids, and derivatives and fragments thereof, comprising a sequence of nucleotides that encodes all or a portion of a polypeptide that binds to IGF-1R, *e.g.*, a nucleic acid encoding all or part of an anti-IGF-1R antibody, 20 antibody fragment, or antibody derivative, plasmids and vectors comprising such nucleic acids, and cells or cell lines comprising such nucleic acids and/or vectors and plasmids. The provided methods include, for example, methods of making, identifying, or isolating molecules that bind to IGF-1R, such as anti-IGF-1R antibodies, methods of determining whether a molecule binds to IGF-1R, methods of determining whether a molecule agonizes or antagonizes IGF-1R, methods of making compositions, such as pharmaceutical 25 compositions, comprising a molecule that binds to IGF-1R, and methods for administering a molecule that binds IGF-1R to a subject, for example, methods for treating a condition mediated by IGF-1R, and for agonizing or antagonizing a biological activity of IGF-1R, IGF-1, and/or IGF-2 *in vivo* or *in vitro*.

30 Polynucleotide and polypeptide sequences are indicated using standard one- or three-letter abbreviations. Unless otherwise indicated, polypeptide sequences have their amino termini at the left and their carboxy termini at the right and single-stranded nucleic acid sequences, and the top strand of double-stranded nucleic acid sequences, have their 5' termini at the left and their 3' termini at the right. A particular polypeptide or polynucleotide sequence also can be described by explaining how it differs from a reference sequence.

35 Polynucleotide and polypeptide sequences of particular light and heavy chain variable domains are shown in Figures 1, 2 and 3,, where they are labeled, for example, L1 ("light chain variable domain 1"), H1 ("heavy chain variable domain 1"), *etc.* Antibodies comprising a light chain and heavy chain from Figures 2 and 3 are indicated by combining the name of the light chain and the name of the heavy chain variable domains. For example, "L4H7," indicates an antibody comprising the light chain variable domain of L4 and the heavy chain variable domain of H7.

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook *et al.* Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

The term "isolated molecule" (where the molecule is, for example, a polypeptide, a polynucleotide, or an antibody) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or synthesized in a cellular system different from the cell from which it naturally originates, will be "isolated" from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The terms "IGF-1R inhibitor" and "IGF-1R antagonist" are used interchangeably. Each is a molecule that detectably inhibits at least one function of IGF-1R. Conversely, an "IGF-1R agonist" is a molecule that detectably increases at least one function of IGF-1R. The inhibition caused by an IGF-1R inhibitor need not be complete so long as it is detectable using an assay. Any assay of a function of IGF-1R can be used, examples of which are provided herein. Examples of functions of IGF-1R that can be inhibited by an IGF-1R inhibitor, or increased by an IGF-1R agonist, include binding to IGF-1, IGF-12, and/or another IGF-1R-activating molecule, kinase activity, downstream signaling, and so on. Examples of types

of IGF-1R inhibitors and IGF-1R agonists include, but are not limited to, IGF-1R binding polypeptides such as antigen binding proteins (e.g., IGF-1R inhibiting antibody binding proteins), antibodies, antibody fragments, and antibody derivatives.

The terms "peptide," "polypeptide" and "protein" each refers to a molecule comprising two or more amino acid residues joined to each other by peptide bonds. These terms encompass, e.g., native and artificial proteins, protein fragments and polypeptide analogs (such as muteins, variants, and fusion proteins) of a protein sequence as well as post-translationally, or otherwise covalently or non-covalently, modified proteins. A peptide, polypeptide, or protein may be monomeric or polymeric.

The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion as compared to a corresponding full-length protein. Fragments can be, for example, at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 50, 70, 80, 90, 100, 150 or 200 amino acids in length. Fragments can also be, for example, at most 1,000, 750, 500, 250, 200, 175, 150, 125, 100, 90, 80, 70, 60, 50, 40, 30, 20, 15, 14, 13, 12, 11, or 10 amino acids in length. A fragment can further comprise, at either or both of its ends, one or more additional amino acids, for example, a sequence of amino acids from a different naturally-occurring protein (e.g., an Fc or leucine zipper domain) or an artificial amino acid sequence (e.g., an artificial linker sequence).

Polypeptides of the invention include polypeptides that have been modified in any way and for any reason, for example, to: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify other physicochemical or functional properties. Analogs include muteins of a polypeptide. For example, single or multiple amino acid substitutions (e.g., conservative amino acid substitutions) may be made in the naturally occurring sequence (e.g., in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A "conservative amino acid substitution" is one that does not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterize the parent sequence or are necessary for its functionality). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton *et al.* *Nature* 354:105 (1991), which are each incorporated herein by reference.

The present invention also provides non-peptide analogs of IGF-1R binding polypeptides. Non-peptide analogs are commonly used in the pharmaceutical industry as drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, J. *Adv. Drug Res.* 15:29 (1986); Veber and Freidinger *TINS* p.392 (1985); and Evans *et al.* *J. Med. Chem.* 30:1229 (1987), which are incorporated herein by reference. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a desired biochemical property or pharmacological activity), such as a human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH<sub>2</sub>NH--, --CH<sub>2</sub>S--, --CH<sub>2</sub>--CH<sub>2</sub>--, --CH=CH-(*cis* and *trans*), --

COCH<sub>2</sub>--, --CH(OH)CH<sub>2</sub>--, and --CH<sub>2</sub>SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch *Ann. Rev. Biochem.* 61:387 (1992), incorporated herein by reference), for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

A "variant" of a polypeptide (*e.g.*, an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants of the invention include fusion proteins.

A "derivative" of a polypeptide is a polypeptide (*e.g.*, an antibody) that has been chemically modified, *e.g.*, via conjugation to another chemical moiety such as, for example, polyethylene glycol, albumin (*e.g.*, human serum albumin), phosphorylation, and glycosylation. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below.

An "antigen binding protein" is a protein comprising a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include antibodies, antibody fragments (*e.g.*, an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, for example, Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129; Roque et al., 2004, *Biotechnol. Prog.* 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronectin components as a scaffold.

An antigen binding protein can have, for example, the structure of a naturally occurring immunoglobulin. An "immunoglobulin" is a tetrameric molecule. In a naturally occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, *Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y.

(1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

Naturally occurring immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *et al.* in *Sequences of Proteins of Immunological Interest*, 5<sup>th</sup> Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991.

An "antibody" refers to an intact immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. Antigen binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, *inter alia*, Fab, Fab', F(ab')<sub>2</sub>, Fv, domain antibodies (dAbs), and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

A Fab fragment is a monovalent fragment having the V<sub>L</sub>, V<sub>H</sub>, C<sub>L</sub> and C<sub>H</sub>1 domains; a F(ab')<sub>2</sub> fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V<sub>H</sub> and C<sub>H</sub>1 domains; an Fv fragment has the V<sub>L</sub> and V<sub>H</sub> domains of a single arm of an antibody; and a dAb fragment has a V<sub>H</sub> domain, a V<sub>L</sub> domain, or an antigen-binding fragment of a V<sub>H</sub> or V<sub>L</sub> domain (US Pat. No. 6,846,634, 6,696,245, US App. Pub. No. 05/0202512, 04/0202995, 04/0038291, 04/0009507, 03/0039958, Ward *et al.*, Nature 341:544-546, 1989).

A single-chain antibody (scFv) is an antibody in which a V<sub>L</sub> and a V<sub>H</sub> region are joined via a linker (*e.g.*, a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (see, *e.g.*, Bird *et al.*, 1988, Science 242:423-26 and Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA 85:5879-83). Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises V<sub>H</sub> and V<sub>L</sub> domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, *e.g.*, Holliger *et al.*, 1993, Proc. Natl. Acad. Sci. USA 90:6444-48, and Poljak *et al.*, 1994, Structure 2:1121-23). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using the system described by Kabat *et al.* in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein. An antigen binding protein may incorporate the CDR(s) as part of a larger

polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

5 An antigen binding protein may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a "bispecific" or "bifunctional" antibody has two different binding sites.

10 The term "human antibody" includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully human antibody). These antibodies may be prepared in a variety of ways, examples of which are described below, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes.

15 A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another  
20 embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are  
25 made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In one embodiment, one or more of  
30 the CDRs are derived from a human anti-IGF-1R antibody. In another embodiment, all of the CDRs are derived from a human anti-IGF-1R antibody. In another embodiment, the CDRs from more than one human anti-IGF-1R antibodies are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-IGF-1R antibody, a CDR2 and a CDR3 from the light chain of a second human anti-IGF-1R antibody, and the CDRs from the heavy chain  
35 from a third anti-IGF-1R antibody. Further, the framework regions may be derived from one of the same anti-IGF-1R antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with, homologous to,  
40 to, or derived from an antibody (-ies) from another species or belonging to another antibody class or

subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (*i.e.*, the ability to specifically bind IGF-1R). See, *e.g.*, U.S. Patent No. 4,816,567 and Morrison, 1985, Science 229:1202-07.

5 A "neutralizing antibody" or "an inhibitory antibody" is an antibody that inhibits the binding of IGF-1R to IGF-I and/or IGF-2 when an excess of the anti-IGF-1R antibody reduces the amount of IGF-I and/or IGF-2 bound to IGF-1R by at least about 20% using the assay described in Example 9. In various embodiments, the antibody reduces the amount of IGF-I and/or IGF-2 bound to IGF-1R by at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, and 99.9%.

10 An "activating antibody" is an antibody that activates IGF-1R by at least about 20% when added to a cell, tissue or organism expressing IGF-1R, where "100% activation" is the level of activation achieved under physiological conditions by the same molar amount of IGF-1 and/or IGF-2. In various embodiments, the antibody activates IGF-1R activity by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 750%, or 1000%.

15 Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification and using techniques well-known in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See, *e.g.*, Bowie *et al.*, 1991, Science 253:164.

20 A "CDR grafted antibody" is an antibody comprising one or more CDRs derived from an antibody of a particular species or isotype and the framework of another antibody of the same or different species or isotype.

25 A "multi-specific antibody" is an antibody that recognizes more than one epitope on one or more antigens. A subclass of this type of antibody is a "bi-specific antibody" which recognizes two distinct epitopes on the same or different antigens.

An antigen binding protein "specifically binds" to an antigen (*e.g.*, human IGF-1R) if it binds to the antigen with a dissociation constant of 1 nanomolar or less.

30 An "antigen binding domain," "antigen binding region," or "antigen binding site" is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody that specifically binds to its antigen, this will include at least part of at least one of its CDR domains.

35 An "epitope" is the portion of a molecule that is bound by an antigen binding protein (*e.g.*, by an antibody). An epitope can comprise non-contiguous portions of the molecule (*e.g.*, in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).



The “percent identity” of two polynucleotide or two polypeptide sequences is determined by comparing the sequences using the GAP computer program (a part of the GCG Wisconsin Package, version 10.3 (Accelrys, San Diego, CA)) using its default parameters.

5 The terms “polynucleotide,” “oligonucleotide” and “nucleic acid” are used interchangeably throughout and include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs (*e.g.*, peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutein, or variant thereof,  
10 of the invention.

Two single-stranded polynucleotides are “the complement” of each other if their sequences can be aligned in an anti-parallel orientation such that every nucleotide in one polynucleotide is opposite its complementary nucleotide in the other polynucleotide, without the introduction of gaps, and without unpaired nucleotides at the 5’ or the 3’ end of either sequence. A polynucleotide is “complementary” to  
15 another polynucleotide if the two polynucleotides can hybridize to one another under moderately stringent conditions. Thus, a polynucleotide can be complementary to another polynucleotide without being its complement.

A “vector” is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a “plasmid,” which refers to a linear or circular double stranded DNA molecule  
20 into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated  
25 into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An “expression vector” is a type of vector that can direct the expression of a chosen polynucleotide.

A nucleotide sequence is “operably linked” to a regulatory sequence if the regulatory sequence affects the expression (*e.g.*, the level, timing, or location of expression) of the nucleotide sequence. A  
30 “regulatory sequence” is a nucleic acid that affects the expression (*e.g.*, the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (*e.g.*, polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation  
35 signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA and Baron *et al.*, 1995, Nucleic Acids Res. 23:3605–06.

A “host cell” is a cell that can be used to express a nucleic acid, *e.g.*, a nucleic acid of the invention. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a  
40 single-celled eukaryote (*e.g.*, a yeast or other fungus), a plant cell (*e.g.*, a tobacco or tomato plant cell), an

animal cell (*e.g.*, a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Examples of host cells include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (see Gluzman *et al.*, 1981, *Cell* 23:175), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (see Rasmussen *et al.*, 1998, *Cytotechnology* 28:31) or CHO strain DX-B11, which is deficient in DHFR (see Urlaub *et al.*, 1980, *Proc. Natl. Acad. Sci. USA* 77:4216-20), HeLa cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (see McMahan *et al.*, 1991, *EMBO J.* 10:2821), human embryonic kidney cells such as 293, 293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase "recombinant host cell" can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to, *e.g.*, mutation or environmental influence, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

#### IGF-1R

IGF-1R is a transmembrane receptor tyrosine kinase (Blume-Jensen *et al.*, 2001, *Nature* 411:355-65). The human IGF-1R is synthesized as a 1367 amino acid precursor polypeptide that includes a 30 amino acid signal peptide removed during translocation into the endoplasmic reticulum (Swiss-Prot: P08069). The IGF-1R proreceptor is glycosylated and cleaved by a protease at positions 708-711 (counting from the first amino acid following the signal peptide sequence) during maturation in the ER-golgi resulting in the formation of an  $\alpha$ -chain (1-707) and a  $\beta$ -chain (712-1337) that remain linked by disulfide bonds (Bhaumick *et al.*, 1981, *Proc Natl Acad Sci USA* 78:4279-83, Chernausek *et al.*, 1981, *Biochemistry* 20:7345-50, Jacobs *et al.*, 1983, *Proc Natl Acad Sci USA* 80:1228-31, LeBon *et al.*, 1986, *J Biol Chem* 261:7685-89, Elleman, *et al.*, 2000, *Biochem J* 347:771-79). The predominant form of the IGF-1R (and INSR) that exists on the cell-surface is a proteolytically processed and glycosylated ( $\alpha\beta$ )<sub>2</sub> dimer joined covalently by one or more disulfide bonds.

The extracellular portion of the IGF-1R consists of the  $\alpha$ -chain and 191 amino acids of the  $\beta$ -chain (712-905). The receptor contains a single transmembrane spanning sequence (906-929) and a 408-residue cytoplasmic domain that includes a functional tyrosine kinase (Rubin *et al.*, 1983, *Nature* 305:438-440). Comparative sequence analysis has revealed that the IGF-1R is composed of 11 distinct structural motifs (reviewed by Adams *et al.*, 2000, *Cell Mol Life Sci* 57:1050-93, Marino-Buslje *et al.*, 1998, *FEBS Ltrs* 441:331-36, Ward *et al.*, 2001, *BMC Bioinformatics* 2:4). The N-terminal half of the extracellular domain contains two homologous domains referred to as L1 (1-151) and L2 (299-461) (Ward *et al.*, 2001, *supra*) separated by a cysteine-rich (CR) region (152-298) consisting of several structural modules with disulfide

linkages that align with repeating units present in the TNF receptor and laminin (Ward *et al.*, 1995, *Proteins* 22:141-53). The crystal structure of the L1—CR-L2 domain has been solved (Garrett *et al.*, 1998, *Nature* 394:395-99). The L2 domain is followed by three fibronectin type III domains (Marino-Buslje *et al.*, 1998, *supra*, Mulhern *et al.*, 1998, *Trends Biochem Sci* 23:465-66, Ward *et al.*, 1999, *Growth Factors* 16:315-22).

5 The first FnIII domain (FnIII-1, 461-579) is 118 amino acids in length. The second FnIII domain (FnIII-2, 580-798) is disrupted by a major insert sequence (ID) of about 120 amino acids in length. The ID domain includes a furin protease cleavage site that separates the  $\alpha$  and  $\beta$  chains of the mature receptor. The third

10 FnIII domain (FnIII-3) is located entirely in the  $\beta$ -chain (799-901) terminating several residues before the transmembrane sequence. The catalytic domain of the IGF-1R tyrosine kinase is located between amino acids positions 973-1229, and its structure has been solved (Favelyukis *et al.*, 2001, *Nature Structural Biol* 8:1058-63, Pautsch *et al.*, 2001, *Structure* 9:955-65). The kinase is flanked by two regulatory regions, the juxtamembrane region (930-972) and a 108 amino acid C-terminal tail (1220-1337) (Surmacz *et al.*, 1995, *Experimental Cell Res* 218:370-80, Hongo *et al.*, 1996, *Oncogene* 12:1231-38). The two regulatory regions contain tyrosine residues that serve as docking sites for signal transducing proteins when phosphorylated by

15 the activated IGF-1R tyrosine kinase (reviewed by Baserga (ed.), 1998 *The IGF-1 Receptor in Normal and Abnormal Growth*, Hormones and Growth Factors in Development and Neoplasia, Wiley-Liss, Inc., Adams *et al.*, 2000, *Cell Mol Life Sci* 57:1050-93).

The IGF-1R amino acid sequence is about 70% identical to the insulin receptor (INSR; Swiss-Prot: P06213). The highest homology between the receptors is located in the tyrosine kinase domain (84%); the

20 lowest identity is in the CR region and the C-terminus. The IGF-1R is also highly related (~ 55% identical) to the insulin related receptor (IRR; Swiss-Prot: P14616).

Human IGF-1R can be activated by the insulin-like growth factors, IGF-1 and IGF-2 and insulin (INS) (Hill *et al.*, 1985, *Pediatric Research* 19:879-86). IGF-1 and IGF-2 are encoded nonallelic genes (Brissenden *et al.*, 1984, *Nature* 310: 781-8, Bell *et al.*, 1985, *Proceedings of the National Academy of*

25 *Sciences of the United States of America* 82: 6450-54), and both genes express alternative proteins related by differential RNA splicing and protein processing. The most common and well-studied mature forms of IGF-1 and IGF-2 are respectively 70 and 67 amino acids in length (Jansen *et al.*, 1983, *Nature* 306:609-11, Dull *et al.*, 1984, *Nature* 310: 777-81). These proteins (and their isoforms) are identical at 11/21 positions to the insulin A-peptide, and identical at 12/30 positions with the insulin B-peptide.

30 IGF-1R is expressed in all cells types in the normal adult animal except for liver hepatocytes and mature B-cells. Human blood plasma contains high concentrations of IGF-1 and IGF-2, and IGF-1 can be detected in most tissues. The receptor is an integral component of the physiological mechanism controlling organ size and homeostasis. Without being bound to a particular theory, the "Somatomedin Hypothesis" states that Growth Hormone (GH) mediated somatic growth that occurs during childhood and adolescence

35 is dependent on the endocrine form of IGF-1 that is mainly produced and secreted by the liver (Daughaday, 2000, *Pediatric Nephrology* 14: 537-40). The synthesis of hepatic IGF-1 is stimulated by GH release in the pituitary in response to hypothalamic GHRH (GH releasing hormone). The serum concentration of IGF-1 increases over 100 fold between ages 5-15 in humans. The bioavailability of IGF-1 is regulated by IGF binding protein 3 (IGFBP3) with approximately 99% of the growth factor compartmentalized in the bound

40 state. Primary IGF-1 deficiency arising from partial gene deletions, and secondary IGF-1 deficiency

resulting from defects in GH production or signaling are not lethal (Woods, 1999, *IGF Deficiency* in Contemporary Endocrinology: The IGF System, R. a. R. Rosenfeld, C. Jr. Totowa, ed.s, Humana Press, NJ: 651-74). The affected individuals exhibit growth retardation at birth, grow slowly and can face certain CNS abnormalities.

- 5 IGF-1R signaling promotes cell growth and survival through the IRS adapter protein-dependent activation of the PI3Kinase/Akt pathway. IGF-1R transmits a signal to its major substrates, IRS-1 through IRS-4 and the Shc proteins (Blakesley *et al.*, 1999, *IGF-1 receptor function: transducing the IGF-1 signal into intracellular events* in The IGF System, R. G. a. R. Rosenfeld, Jr. C.T. Totowa, ed.s, Humana Press, NJ: 143-63). This results in activation of the Ras/Raf/MAP kinase and PI3 Kinase/Akt signaling pathways.
- 10 However, induction of Akt-mediated cell survival via IRS is the dominant pathway response upon IGF stimulation of most cells. See Figure 10.

#### Antigen binding proteins

- 15 In one aspect, the present invention provides antigen binding proteins (*e.g.*, antibodies, antibody fragments, antibody derivatives, antibody muteins, and antibody variants), that bind to IGF-1R, *e.g.*, human IGF-1R.

- Antigen binding proteins in accordance with the present invention include antigen binding proteins that inhibit a biological activity of IGF-1R. Examples of such biological activities include binding a signaling molecule (*e.g.*, IGF-1 and/or IGF-2), and transducing a signal in response to binding a signaling molecule.
- 20

- Different antigen binding proteins may bind to different domains or epitopes of IGF-1R or act by different mechanisms of action. Examples include but are not limited to antigen binding proteins that interfere with binding of IGF-1 and/or IGF-2 to IGF-1R or that inhibit signal transduction. The site of action may be, for example, intracellular (*e.g.*, by interfering with an intracellular signaling cascade) or extracellular. An antigen binding protein need not completely inhibit an IGF-1 and/or IGF-2 induced activity to find use in the present invention; rather, antigen binding proteins that reduce a particular activity of IGF-1 and/or IGF-2 are contemplated for use as well. (Discussions herein of particular mechanisms of action for IGF-1R-binding antigen binding proteins in treating particular diseases are illustrative only, and the methods presented herein are not bound thereby.)
- 25

- 30 It has been observed that IGF-1 and IGF-2 each exhibits biphasic binding to IGF-1R. High affinity binding has been reported to have a  $K_D$  in the range of 0.2 nM; high affinity binding, about ten fold higher. Thus, in one embodiment, the present invention provides an IGF-1R inhibitor that inhibits both the high and low affinity binding of IGF-1 and/or IGF-2 to IGF-R. It has been suggested that the high affinity binding, rather than the low affinity binding, of IGF-1 and/or IGF-2 to IGF-1R is required for the conformation change that activates the tyrosine kinase activity of IGF-1R. Thus, in another embodiment, the IGF-1R inhibitor preferentially inhibits the high affinity binding of IGF-1 and/or IGF-2 to IGF-1R as compared to the low affinity binding.
- 35

- In another aspect, the present invention provides antigen binding proteins that comprise a light chain variable region selected from the group consisting of L1 through L52 and/or a heavy chain variable region selected from the group consisting of H1 through H52, and fragments, derivatives, muteins, and
- 40

variants thereof (see Figures 2 and 3). Such an antigen binding protein can be denoted using the nomenclature "LxHy", wherein "x" corresponds to the number of the light chain variable region and "y" corresponds to the number of the heavy chain variable region as they are labeled in Figures 2 and 3. For example, L2H1 refers to an antigen binding protein with a light chain variable region comprising the amino acid sequence of L2 and a heavy chain variable region comprising the amino acid sequence of H1, as shown in Figures 2 and 3. Figures 2 and 3 also indicate the location of the CDR and framework regions of each of these variable domain sequences. The CDR regions of each light and heavy chain also are grouped by type and by sequence similarity in Figures 4 through 9. Antigen binding proteins of the invention include, for example, antigen binding proteins having a combination of light chain and heavy chain variable domains selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52.

In one embodiment, the present invention provides an antigen binding protein comprising a light chain variable domain comprising a sequence of amino acids that differs from the sequence of a light chain variable domain selected from the group consisting of L1 through L52 only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residues, wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the light-chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to a nucleotide sequence that encodes a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to a complement of a light chain polynucleotide selected from Figure 1.

In another embodiment, the present invention provides an antigen binding protein comprising a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of a heavy chain variable domain selected from the group consisting of H1 through H52 only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residue(s), wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%,

97%, or 99% identical to the sequence of a heavy chain variable domain selected from the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to a nucleotide sequence that encodes a heavy chain variable domain selected from the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a heavy chain variable domain selected from the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a heavy chain variable domain selected from the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to a complement of a heavy chain polynucleotide selected from Figure 1.

Particular embodiments of antigen binding proteins of the present invention comprise one or more amino acid sequences that are identical to the amino acid sequences of one or more of the CDRs and/or FRs illustrated in Figures 2 through 9. In one embodiment, the antigen binding protein comprises a light chain CDR1 sequence illustrated in Figure 4. In another embodiment, the antigen binding protein comprises a light chain CDR2 sequence illustrated in Figure 5. In another embodiment, the antigen binding protein comprises a light chain CDR3 sequence illustrated in Figure 6. In another embodiment, the antigen binding protein comprises a heavy chain CDR1 sequence illustrated in Figure 7. In another embodiment, the antigen binding protein comprises a heavy chain CDR2 sequence illustrated in Figure 8. In another embodiment, the antigen binding protein comprises a heavy chain CDR3 sequence illustrated in Figure 9. In another embodiment, the antigen binding protein comprises a light chain FR1 sequence illustrated in Figure 2. In another embodiment, the antigen binding protein comprises a light chain FR2 sequence illustrated in Figure 2. In another embodiment, the antigen binding protein comprises a light chain FR3 sequence illustrated in Figure 2. In another embodiment, the antigen binding protein comprises a light chain FR4 sequence illustrated in Figure 2. In another embodiment, the antigen binding protein comprises a heavy chain FR1 sequence illustrated in Figure 3. In another embodiment, the antigen binding protein comprises a heavy chain FR2 sequence illustrated in Figure 3. In another embodiment, the antigen binding protein comprises a heavy chain FR3 sequence illustrated in Figure 3. In another embodiment, the antigen binding protein comprises a heavy chain FR4 sequence illustrated in Figure 3.

In one embodiment, the present invention provides an antigen binding protein that comprises one or more CDR sequences that differ from a CDR sequence shown in Figures 2 through 9 by no more than 5, 4, 3, 2, or 1 amino acid residues.

In one embodiment, the present invention provides an antigen binding protein that comprises at least one CDR from L1-L52 and/or H1-H52, as shown in Figures 2 through 9, and at least one CDR sequence from an anti-IGF-1R antibody described in US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO

05/016970, or WO 05/058967 (each of which is incorporated herein by reference in its entirety for all purposes) wherein the antigen binding protein binds to IGF-1 receptor. In another embodiment, the antigen binding protein comprises 2, 3, 4, or 5 CDR sequences from L1-L52 and/or H1-H52, as shown in Figures 2 through 9. In another embodiment, the antigen binding protein comprises 2, 3, 4, or 5 CDR sequences from an anti-IGF-1R antibody described in US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967. In another embodiment, at least one of the antigen binding protein's CDR3 sequences is a CDR3 sequence from L1-L52 and/or H1-H52, as shown in Figures 2, 3, 6, and 9. In another embodiment, the antigen binding protein's light chain CDR3 sequence is a light chain CDR3 sequence from L1-L52 as shown in Figures 2 and 6 and the antigen binding protein's heavy chain CDR3 sequence is a heavy chain sequence from H1-H52 as shown in Figures 3 and 9. In another embodiment, the antigen binding protein comprises 1, 2, 3, 4, or 5 CDR sequences that each independently differs by 6, 5, 4, 3, 2, 1, or 0 single amino acid additions, substitutions, and/or deletions from a CDR sequence of L1-L52 and/or H1-H52, and the antigen binding protein further comprises 1, 2, 3, 4, or 5 CDR sequences that each independently differs by 6, 5, 4, 3, 2, 1, or 0 single amino acid additions, substitutions, and/or deletions from a CDR sequence of US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967. In another embodiment, the CDR sequence(s) from US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967. In another embodiment, the CDR sequence(s) are from (an) antibody(-ies) that bind(s) to the L2 portion of the extracellular domain of IGF-1 receptor. In another embodiment, the antigen binding protein does not comprise a light chain CDR3 sequence and/or a heavy chain CDR3 sequence from an anti-IGF-1R antibody from US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967.

In one embodiment, the present invention provides an antigen binding protein that comprises a light chain CDR1 comprising the sequence RSSQSLHX<sub>1</sub>X<sub>2</sub>GYNX<sub>3</sub>LX<sub>4</sub> (SEQ ID NO:236), wherein X<sub>1</sub> is a serine or a threonine residue, X<sub>2</sub> is an asparagine, serine, or histidine residue, X<sub>3</sub> is a tyrosine or a phenylalanine residue, and X<sub>4</sub> is an aspartate or an asparagine residue. In another embodiment, the light chain CDR1 comprises the sequence TRSSGX<sub>1</sub>IX<sub>2</sub>X<sub>3</sub>NYVQ (SEQ ID NO:237), wherein X<sub>1</sub> is a serine or an aspartate residue, X<sub>2</sub> is an alanine or an aspartate residue, and X<sub>3</sub> is a serine or an asparagine residue. In another embodiment, the light chain CDR1 comprises the sequence RASQX<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub>LX<sub>6</sub> (SEQ ID NO:238), wherein X<sub>1</sub> is a glycine or a serine residue, X<sub>2</sub> is an isoleucine, valine, or proline residue, and X<sub>3</sub> is a serine, glycine, or tyrosine residue, X<sub>4</sub> is any amino acid residue, X<sub>5</sub> is a phenylalanine, tyrosine, asparagine, or tryptophan residue, and X<sub>6</sub> is an alanine or an asparagine residue. In another embodiment, X<sub>2</sub> is an isoleucine or valine residue, X<sub>3</sub> is a glycine or serine residue, X<sub>4</sub> is an arginine, serine, asparagine, serine, tyrosine, or isoleucine residue, and X<sub>5</sub> is a phenylalanine or a tyrosine residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a light chain CDR2 comprising the sequence  $LX_1X_2X_3RX_4S$  (SEQ ID NO:239), wherein  $X_1$  is a glycine or a valine residue,  $X_2$  is a serine or a phenylalanine residue,  $X_3$  is an asparagine, tyrosine, or threonine residue, and  $X_4$  is an alanine or an aspartate residue. In another embodiment, the CDR2 comprises the sequence  $AX_1SX_2LX_3S$  (SEQ ID NO:240), wherein  $X_1$  is an alanine or a threonine residue,  $X_2$  is a threonine or a glycine residue, and  $X_3$  is a glutamine or a glutamate residue. In another embodiment, the CDR2 comprises the sequence  $X_1X_2NX_3RPS$  (SEQ ID NO:241), wherein  $X_1$  is a glutamate, glutamine, or glycine residue,  $X_2$  is an aspartate or lysine residue, and  $X_3$  is any amino acid residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a light chain CDR3 comprising the sequence  $MX_1X_2X_3X_4X_5PX_6X_7$  (SEQ ID NO:242), wherein  $X_1$  is a glutamine or glutamate residue,  $X_2$  is an alanine, glycine, serine, or threonine residue,  $X_3$  is a leucine or threonine residue,  $X_4$  is a glutamine, glutamate, or histidine residue,  $X_5$  is a threonine, tryptophan, methionine, or valine residue,  $X_6$  is a nonpolar side chain residue, and  $X_7$  is a threonine, serine, or alanine residue. In another embodiment, the CDR3 comprises the sequence  $QXX_1X_2X_3X_4PX_5T$  (SEQ ID NO:243), wherein  $X_1$  is an arginine, serine, leucine, or alanine residue,  $X_2$  is an asparagine, serine, or histidine residue,  $X_3$  is a serine or an asparagine residue,  $X_4$  is a nonpolar side chain residue, and  $X_5$  is a leucine, isoleucine, tyrosine, or tryptophan residue. In another embodiment, the CDR3 comprises the sequence  $QSYX_1SX_2NX_3X_4V$  (SEQ ID NO:244), wherein  $X_1$  is an aspartate or a glutamine residue,  $X_2$  is a serine or an aspartate residue,  $X_3$  is a glutamine, valine, or tryptophan residue, and  $X_4$  is an arginine residue or no residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a heavy chain CDR1 comprising the sequence  $X_1X_2X_3WWS$  (SEQ ID NO:245), wherein  $X_1$  is a serine residue or no residue,  $X_2$  is a serine or asparagine residue, and  $X_3$  is an asparagine residue and an isoleucine residue. In another embodiment, the heavy chain CDR1 comprises the sequence  $X_1X_2YWS$  (SEQ ID NO:246), wherein  $X_1$  is a glycine, asparagine, or aspartate residue, and  $X_2$  is a tyrosine or phenylalanine residue. In another embodiment, the heavy chain CDR1 comprises the sequence  $SYX_1X_2X_3$  (SEQ ID NO:247), wherein  $X_1$  is an alanine or glycine residue,  $X_2$  is a methionine or isoleucine residue, and  $X_3$  is a serine or histidine residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a heavy chain CDR2 comprising the sequence  $X_1X_2X_3X_4X_5GX_6TX_7YNPSLX_8S$  (SEQ ID NO:248), wherein  $X_1$  is a glutamate, tyrosine, or serine residue,  $X_2$  is a isoleucine or valine residue,  $X_3$  is a tyrosine, asparagine, or serine residue,  $X_4$  is a histidine, tyrosine, aspartate, or proline residue,  $X_5$  is a serine or arginine residue,  $X_6$  is a serine or asparagine residue,  $X_7$  is an asparagine or tyrosine residue, and  $X_8$  is a lysine or glutamate residue. In another embodiment, the heavy chain CDR2 comprises the sequence  $X_1ISX_2X_3X_4X_5X_6X_7YYADSVKG$  (SEQ ID NO:249), wherein  $X_1$  is a threonine, alanine, valine, or tyrosine residue,  $X_2$  is a glycine, serine, or tyrosine residue,  $X_3$  is a serine, asparagine, or aspartate residue,  $X_4$  is a glycine or serine residue,  $X_5$  is a glycine, serine, or aspartate residue,  $X_6$  is a serine, threonine, or asparagine residue, and  $X_7$  is a threonine, lysine, or isoleucine residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a heavy chain CDR3 comprising the sequence  $X_1X_2X_3X_4X_5X_6X_7X_8X_9FDI$  (SEQ ID NO:250), wherein  $X_1$  is a



glutamate residue or no residue, X<sub>2</sub> is tyrosine, glycine, or serine residue or no residue, X<sub>3</sub> is a serine, asparagine, tryptophan, or glutamate residue, or no residue, X<sub>4</sub> is a serine, aspartate, tryptophan, alanine, arginine, threonine, glutamine, leucine, or glutamate residue, or no residue, X<sub>5</sub> is a serine, glycine, asparagine, threonine, tryptophan, alanine, valine, or isoleucine residue, X<sub>6</sub> is an arginine, glutamine, tyrosine, valine, alanine, glycine, serine, phenylalanine, or tryptophan residue, X<sub>7</sub> is a leucine, asparagine, aspartate, threonine, tryptophan, tyrosine, valine, alanine, or histidine residue, X<sub>8</sub> is an aspartate, serine, asparagine, or glutamine residue, and X<sub>9</sub> is an alanine or a proline residue. In another embodiment, the heavy chain CDR3 comprises the sequence X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub>X<sub>6</sub>X<sub>7</sub>X<sub>8</sub>X<sub>9</sub>X<sub>10</sub>X<sub>11</sub>MDV (SEQ ID NO:251), wherein X<sub>1</sub> is an alanine residue, or no residue, X<sub>2</sub> is a glutamate, tyrosine, or glycine residue, or no residue, X<sub>3</sub> is a serine or arginine residue, or no residue, X<sub>4</sub> is an aspartate, glycine, serine, or valine residue, or no residue, X<sub>5</sub> is a serine, glycine, or aspartate residue, or no residue, X<sub>6</sub> is a glycine, phenylalanine, aspartate, serine, tryptophan, or tyrosine residue, or no residue, X<sub>7</sub> is a tyrosine, tryptophan, serine, or aspartate residue, or no residue, X<sub>8</sub> is an aspartate, arginine, serine, glycine, tyrosine, or tryptophan residue, X<sub>9</sub> is a tyrosine, isoleucine, leucine, phenylalanine, or lysine residue, X<sub>10</sub> is a tyrosine, phenylalanine, aspartate, or glycine residue, and X<sub>11</sub> is a glycine, tyrosine, or asparagine residue. In another embodiment, the heavy chain CDR3 comprises the sequence X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub>X<sub>6</sub>X<sub>7</sub>X<sub>8</sub>X<sub>9</sub>X<sub>10</sub>Y (SEQ ID NO:252), wherein X<sub>1</sub> is an aspartate or valine residue, or no residue, X<sub>2</sub> is a glycine, tyrosine, arginine, or aspartate residue, or no residue, X<sub>3</sub> is an asparagine, leucine, glycine, isoleucine, serine, valine, phenylalanine, or tyrosine residue, or no residue, X<sub>4</sub> is a leucine, serine, tryptophan, alanine, tyrosine, isoleucine, glycine, or aspartate residue, or no residue, X<sub>5</sub> is a glycine, alanine, tyrosine, serine, aspartate, or leucine residue, X<sub>6</sub> is a valine, alanine, glycine, threonine, proline, histidine, or glutamine residue, X<sub>7</sub> is a glutamate, glycine, serine, aspartate, glycine, valine, tryptophan, histidine, or arginine residue, X<sub>8</sub> is a glutamine, alanine, glycine, tyrosine, proline, leucine, aspartate, or serine residue, X<sub>9</sub> is a nonpolar side chain residue, and X<sub>10</sub> is an aspartate or alanine residue. In another embodiment, the heavy chain CDR3 comprises the sequence X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub>X<sub>6</sub>X<sub>7</sub>X<sub>8</sub>X<sub>9</sub>X<sub>10</sub>YFDX<sub>11</sub> (SEQ ID NO:253), wherein X<sub>1</sub> is a glycine residue, or no residue, X<sub>2</sub> is a proline residue, or no residue, X<sub>3</sub> is an arginine or aspartate residue, or no residue, X<sub>4</sub> is a histidine or proline residue, X<sub>5</sub> is an arginine or glycine residue, X<sub>6</sub> is an arginine, serine, or phenylalanine residue, X<sub>7</sub> is an aspartate or serine residue, X<sub>8</sub> is a glycine, tryptophan, or tyrosine residue, X<sub>9</sub> is a tyrosine or alanine residue, X<sub>10</sub> is an asparagine or tryptophan residue, and X<sub>11</sub> is an asparagine or leucine residue. In another embodiment, the heavy chain CDR3 comprises the sequence X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>DSSX<sub>5</sub>X<sub>6</sub>X<sub>7</sub>X<sub>8</sub>X<sub>9</sub>X<sub>10</sub>X<sub>11</sub>X<sub>12</sub> (SEQ ID NO:254), wherein X<sub>1</sub> is a phenylalanine residue, or no residue, X<sub>2</sub> is an asparagine or glycine residue, or no residue, X<sub>3</sub> is a tyrosine or a leucine residue, or no residue, X<sub>4</sub> is a tyrosine or glycine residue, or no residue, X<sub>5</sub> is a glycine, serine, or valine residue, X<sub>6</sub> is a tyrosine, phenylalanine, tryptophan, or glutamine residue, or no residue, X<sub>7</sub> is a tyrosine, glycine, or isoleucine residue, or no residue, X<sub>8</sub> is a tyrosine, leucine, or glycine residue, or no residue, X<sub>9</sub> is a methionine, glycine, or phenylalanine residue, or no residue, X<sub>10</sub> is an aspartate or methionine residue, or no residue, X<sub>11</sub> is a valine, aspartate, or tyrosine residue, or no residue, and X<sub>12</sub> is a valine residue, or no residue.

In one embodiment, the present invention provides an isolated antigen binding protein, comprising either: a. a light chain CDR3 comprising a sequence selected from the group consisting of: i. a light chain CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L52 as shown

in Figure 6; ii. MQALQTPZT; iii. QQ(R/S)(N/S)(S/N)ZPLT; and iv. QSYDSSNXJV; b. a heavy chain CDR3 comprising a sequence selected from the group consisting of: i. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, or deletions from a CDR3 sequence selected from the group consisting of the heavy chain CDR3 sequences of H1-H52 as shown in Figure 9; ii. SRLDAFDI; iii. SXYDYYGMDV; iv. HRXDXAWYFDL; and v. DSSG; or c. the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b); wherein amino acid residue symbols enclosed in parentheses identify alternative residues for the same position in a sequence, each X is independently any amino acid residue, each Z is independently a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue, each J is independently a glutamine residue, an arginine residue, a valine residue, or a tryptophan residue, and the antigen binding protein binds to human IGF-1R.

The nucleotide sequences of Figure 1, or the amino acid sequences of Figures 2 through 9, can be altered, for example, by random mutagenesis or by site-directed mutagenesis (*e.g.*, oligonucleotide-directed site-specific mutagenesis) to create an altered polynucleotide comprising one or more particular nucleotide substitutions, deletions, or insertions as compared to the non-mutated polynucleotide. Examples of techniques for making such alterations are described in Walder *et al.*, 1986, *Gene* 42:133; Bauer *et al.* 1985, *Gene* 37:73; Craik, *BioTechniques*, January 1985, 12-19; Smith *et al.*, 1981, *Genetic Engineering: Principles and Methods*, Plenum Press; and U.S. Patent Nos. 4,518,584 and 4,737,462. These and other methods can be used to make, for example, derivatives of anti-IGF-1R antibodies that have a desired property, for example, increased affinity, avidity, or specificity for IGF-1R, increased activity or stability *in vivo* or *in vitro*, or reduced *in vivo* side-effects as compared to the underivatized antibody.

Other derivatives of anti-IGF-1R antibodies within the scope of this invention include covalent or aggregative conjugates of anti-IGF-1R antibodies, or fragments thereof, with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an anti-IGF-1R antibody polypeptide. For example, the conjugated peptide may be a heterologous signal (or leader) polypeptide, *e.g.*, the yeast alpha-factor leader, or a peptide such as an epitope tag. Antigen binding protein-containing fusion proteins can comprise peptides added to facilitate purification or identification of antigen binding protein (*e.g.*, poly-His). An antigen binding protein also can be linked to the FLAG peptide Asp-Tyr-Lys-Asp-Asp-Asp-Lys (DYKDDDDK) (SEQ ID NO:255) as described in Hopp *et al.*, *Bio/Technology* 6:1204, 1988, and U.S. Patent 5,011,912. The FLAG peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody (mAb), enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, MO).

Oligomers that contain one or more antigen binding proteins may be employed as IGF-1R antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more antigen binding protein are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, *etc.*

One embodiment is directed to oligomers comprising multiple antigen binding proteins joined *via* covalent or non-covalent interactions between peptide moieties fused to the antigen binding proteins. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of antigen binding proteins attached thereto, as described in more detail below.

In particular embodiments, the oligomers comprise from two to four antigen binding proteins. The antigen binding proteins of the oligomer may be in any form, such as any of the forms described above, *e.g.*, variants or fragments. Preferably, the oligomers comprise antigen binding proteins that have IGF-1R binding activity.

In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, *e.g.*, by Ashkenazi *et al.*, 1991, PNAS USA 88:10535; Byrn *et al.*, 1990, Nature 344:677; and Hollenbaugh *et al.*, 1992 "Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1 - 10.19.11.

One embodiment of the present invention is directed to a dimer comprising two fusion proteins created by fusing an IGF-1R binding fragment of an anti-IGF-1R antibody to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 (hereby incorporated by reference), is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Patent 5,457,035 and in Baum *et al.*, 1994, EMBO J. 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

In other embodiments, the variable portion of the heavy and/or light chains of an anti-IGF-1R antibody may be substituted for the variable portion of an antibody heavy and/or light chain.

Alternatively, the oligomer is a fusion protein comprising multiple antigen binding proteins, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233.

Another method for preparing oligomeric antigen binding proteins involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found.

Leucine zippers were originally identified in several DNA-binding proteins (Landschulz *et al.*, 1988, Science 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe *et al.*, 1994, FEBS Letters 344:191, hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow *et al.*, 1994, Semin. Immunol. 6:267-78. In one approach, recombinant fusion proteins comprising an anti- IGF-1R antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric anti- IGF-1R antibody fragments or derivatives that form are recovered from the culture supernatant.

In one aspect, the present invention provides antigen binding proteins that interfere with the binding of IGF-1 and/or IGF-2 to an IGF-1R. Such antigen binding proteins can be made against IGF-1R, or a fragment, variant or derivative thereof, and screened in conventional assays for the ability to interfere with binding of IGF-1 and/or IGF-2 to IGF-1R. Examples of suitable assays are assays that test the antigen binding proteins for the ability to inhibit binding of IGF-1 and/or IGF-2 to cells expressing IGF-1R, or that test antigen binding proteins for the ability to reduce a biological or cellular response that results from the binding of IGF-1 and/or IGF-2 to cell surface IGF-1R receptors.

In another aspect, the present invention provides an antigen binding protein that blocks the binding of IGF-1 and/or IGF-2 to IGF-1R but does not significantly block the binding of insulin to insulin receptor (INS-R). In one embodiment, the antigen binding protein does not bind to INS-R. In another embodiment, the antigen binding protein binds to the INS-R with such a low affinity that it does not effectively block the binding of insulin to INS-R. In another embodiment, the antigen binding protein binds to INS-R, but antigen binding protein-bound INS-R can still bind to insulin. In another embodiment, the antigen binding protein's selectivity for IGF-1R is at least 50 times greater than its selectivity for insulin receptor. In another embodiment, the selectivity of the antigen binding protein is more than 100 times greater than its selectivity for insulin receptor.

In another aspect, the present invention provides an antigen binding protein that demonstrates species selectivity. In one embodiment, the antigen binding protein binds to one or more mammalian IGF-1R, for example, to human IGF-1R and one or more of mouse, rat, guinea pig, hamster, gerbil, cat, rabbit, dog, goat, sheep, cow, horse, camel, and non-human primate IGF-1R. In another embodiment, the antigen binding protein binds to one or more primate IGF-1R, for example, to human IGF-1R and one or more of cynomologous, marmoset, rhesus, and chimpanzee IGF-1R. In another embodiment, the antigen binding protein binds specifically to human, cynomologous, marmoset, rhesus, or chimpanzee IGF-1R. In another embodiment, the antigen binding protein does not bind to one or more of mouse, rat, guinea pig, hamster, gerbil, cat, rabbit, dog, goat, sheep, cow, horse, camel, and non-human primate IGF-1R. In another embodiment, the antigen binding protein does not bind to a New World monkey species such as a marmoset. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than IGF-1R. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than mammalian IGF-1R. In another

embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than primate IGF-1R. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than human IGF-1R. In another embodiment, the antigen binding protein specifically binds to mouse, rat, cynomolgus monkey, and human IGF-1R. In another embodiment, the antigen binding protein specifically binds to mouse, rat, cynomolgus monkey, and human IGF-1R with a similar binding affinity. In another embodiment, the antigen binding protein blocks binding of human IGF-1 and IGF-2 with mouse, rat, cynomolgus monkey, and human IGF-1R. In another embodiment, the antigen binding protein blocks binding of human IGF-1 and IGF-2 with mouse, rat, cynomolgus monkey, and human IGF-1R with similar  $K_i$ . In another embodiment, the antigen binding protein blocks binding of human IGF-1 and IGF-2 with mouse, rat, cynomolgus monkey, and human IGF-1R with a  $K_i$  of between about 0.57 and about 0.61 nM.

One may determine the selectivity of an antigen binding protein for an IGF-1R using methods well known in the art and following the teachings of the specification. For example, one may determine the selectivity using Western blot, FACS, ELISA or RIA.

In another aspect, the present invention provides an IGF-1R binding antigen binding protein (for example, an anti-IGF-1R antibody), that has one or more of the following characteristics: binds to both human and murine IGF-1R, inhibits the binding of both IGF-1 and IGF-2 to human IGF-1R, inhibits the binding of both IGF-1 and IGF-2 to murine IGF-1R, preferentially inhibits the high affinity binding of IGF-1 and/or of IGF-2 to IGF-1R, binds to the L2 domain of IGF-1R, causes relatively little down-regulation of cell-surface expressed IGF-1R after 17 hours of exposure (as compared to MAB391 (R&D systems, Minneapolis, MN); e.g., amount of IGF-1R is reduced by less than 20%), causes a level of down-regulation of cell-surface expressed IGF-1R on Colo-205 or MiaPaCa-2 xenograft tumor cells in mice as MAB391 after four weeks of once weekly doses of 200 micrograms.

Antigen-binding fragments of antigen binding proteins of the invention may be produced by conventional techniques. Examples of such fragments include, but are not limited to, Fab and  $F(ab')_2$  fragments. Antibody fragments and derivatives produced by genetic engineering techniques also are contemplated.

Additional embodiments include chimeric antibodies, e.g., humanized versions of non-human (e.g., murine) monoclonal antibodies. Such humanized antibodies may be prepared by known techniques, and offer the advantage of reduced immunogenicity when the antibodies are administered to humans. In one embodiment, a humanized monoclonal antibody comprises the variable domain of a murine antibody (or all or part of the antigen binding site thereof) and a constant domain derived from a human antibody. Alternatively, a humanized antibody fragment may comprise the antigen binding site of a murine monoclonal antibody and a variable domain fragment (lacking the antigen-binding site) derived from a human antibody. Procedures for the production of chimeric and further engineered monoclonal antibodies include those described in Riechmann *et al.*, 1988, Nature 332:323, Liu *et al.*, 1987, Proc. Nat. Acad. Sci. USA 84:3439, Larrick *et al.*, 1989, Bio/Technology 7:934, and Winter *et al.*, 1993, TIPS 14:139. In one embodiment, the chimeric antibody is a CDR grafted antibody. Techniques for humanizing antibodies are discussed in, e.g., U.S. Pat. App. No. 10/194,975 (published February 27, 2003), U.S. Pat. No.s 5,869,619,

5,225,539, 5,821,337, 5,859,205, Padlan *et al.*, 1995, FASEB J. 9:133-39, and Tamura *et al.*, 2000, J. Immunol. 164:1432-41.

Procedures have been developed for generating human or partially human antibodies in non-human animals. For example, mice in which one or more endogenous immunoglobulin genes have been inactivated by various means have been prepared. Human immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes. Antibodies produced in the animal incorporate human immunoglobulin polypeptide chains encoded by the human genetic material introduced into the animal. In one embodiment, a non-human animal, such as a transgenic mouse, is immunized with an IGF-1R polypeptide, such that antibodies directed against the IGF-1R polypeptide are generated in the animal. One example of a suitable immunogen is a soluble human IGF-1R, such as a polypeptide comprising the extracellular domain of the protein of Figure 10, or other immunogenic fragment of the protein of Figure 10. Examples of techniques for production and use of transgenic animals for the production of human or partially human antibodies are described in U.S. Patents 5,814,318, 5,569,825, and 5,545,806, Davis *et al.*, 2003, *Production of human antibodies from transgenic mice* in Lo, ed. *Antibody Engineering: Methods and Protocols*, Humana Press, NJ:191-200, Kellermann *et al.*, 2002, *Curr Opin Biotechnol.* 13:593-97, Russel *et al.*, 2000, *Infect Immun.* 68:1820-26, Gallo *et al.*, 2000, *Eur J Immun.* 30:534-40, Davis *et al.*, 1999, *Cancer Metastasis Rev.* 18:421-25, Green, 1999, *J Immunol Methods.* 231:11-23, Jakobovits, 1998, *Advanced Drug Delivery Reviews* 31:33-42, Green *et al.*, 1998, *J Exp Med.* 188:483-95, Jakobovits A, 1998, *Exp. Opin. Invest. Drugs.* 7:607-14, Tsuda *et al.*, 1997, *Genomics.* 42:413-21, Mendez *et al.*, 1997, *Nat Genet.* 15:146-56, Jakobovits, 1994, *Curr Biol.* 4:761-63, Arbones *et al.*, 1994, *Immunity.* 1:247-60, Green *et al.*, 1994, *Nat Genet.* 7:13-21, Jakobovits *et al.*, 1993, *Nature.* 362:255-58, Jakobovits *et al.*, 1993, *Proc Natl Acad Sci U S A.* 90:2551-55. Chen, J., M. Trounstine, F. W. Alt, F. Young, C. Kurahara, J. Loring, D. Huszar. "Immunoglobulin gene rearrangement in B cell deficient mice generated by targeted deletion of the JH locus." *International Immunology* 5 (1993): 647-656, Choi *et al.*, 1993, *Nature Genetics* 4: 117-23, Fishwild *et al.*, 1996, *Nature Biotechnology* 14: 845-51, Harding *et al.*, 1995, *Annals of the New York Academy of Sciences*, Lonberg *et al.*, 1994, *Nature* 368: 856-59, Lonberg, 1994, *Transgenic Approaches to Human Monoclonal Antibodies* in *Handbook of Experimental Pharmacology* 113: 49-101, Lonberg *et al.*, 1995, *Internal Review of Immunology* 13: 65-93, Neuberger, 1996, *Nature Biotechnology* 14: 826, Taylor *et al.*, 1992, *Nucleic Acids Research* 20: 6287-95, Taylor *et al.*, 1994, *International Immunology* 6: 579-91, Tomizuka *et al.*, 1997, *Nature Genetics* 16: 133-43, Tomizuka *et al.*, 2000, *Proceedings of the National Academy of Sciences USA* 97: 722-27, Tuaillon *et al.*, 1993, *Proceedings of the National Academy of Sciences USA* 90: 3720-24, and Tuaillon *et al.*, 1994, *Journal of Immunology* 152: 2912-20.

In another aspect, the present invention provides monoclonal antibodies that bind to IGF-1R. Monoclonal antibodies may be produced using any technique known in the art, *e.g.*, by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, *e.g.*, by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-

X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

In one embodiment, a hybridoma cell line is produced by immunizing an animal (e.g., a transgenic animal having human immunoglobulin sequences) with an IGF-1R immunogen; harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that binds an IGF-1R polypeptide. Such hybridoma cell lines, and anti-IGF-1R monoclonal antibodies produced by them, are encompassed by the present invention.

Monoclonal antibodies secreted by a hybridoma cell line can be purified using any technique known in the art. Hybridomas or mAbs may be further screened to identify mAbs with particular properties, such as the ability to block an IGF-1 and/or IGF-2 induced activity. Examples of such screens are provided in the examples below.

Molecular evolution of the complementarity determining regions (CDRs) in the center of the antibody binding site also has been used to isolate antibodies with increased affinity, for example, antibodies having increased affinity for c-erbB-2, as described by Schier *et al.*, 1996, J. Mol. Biol. 263:551. Accordingly, such techniques are useful in preparing antibodies to IGF-1R.

Antigen binding proteins directed against an IGF-1R can be used, for example, in assays to detect the presence of IGF-1R polypeptides, either *in vitro* or *in vivo*. The antigen binding proteins also may be employed in purifying IGF-1R proteins by immunoaffinity chromatography. Those antigen binding proteins that additionally can block binding of IGF-1 and/or IGF-2 to IGF-1R may be used to inhibit a biological activity that results from such binding. Blocking antigen binding proteins can be used in the methods of the present invention. Such antigen binding proteins that function as IGF-1 and/or IGF-2 antagonists may be employed in treating any IGF-1 and/or IGF-2-induced condition, including but not limited to cancer. In one embodiment, a human anti-IGF-1R monoclonal antibody generated by procedures involving immunization of transgenic mice is employed in treating such conditions.

Antigen binding proteins may be employed in an *in vitro* procedure, or administered *in vivo* to inhibit an IGF-1 and/or IGF-2-induced biological activity. Disorders caused or exacerbated (directly or indirectly) by the interaction of IGF-1 and/or IGF-2 with cell surface IGF-1R, examples of which are provided above, thus may be treated. In one embodiment, the present invention provides a therapeutic method comprising *in vivo* administration of an IGF-1 and/or IGF-2 blocking antigen binding protein to a mammal in need thereof in an amount effective for reducing an IGF-1 and/or IGF-2-induced biological activity.

Antigen binding proteins of the invention include partially human and fully human monoclonal antibodies that inhibit a biological activity of IGF-1 and also inhibit a biological activity of IGF-2. One embodiment is directed to a human monoclonal antibody that at least partially blocks binding of IGF-1 and of IGF-2 to a cell that expresses human IGF-1R. In one embodiment, the antibodies are generated by immunizing a transgenic mouse with an IGF-1R immunogen. In another embodiment, the immunogen is a human IGF-1R polypeptide (e.g., a soluble fragment comprising all or part of the IGF-1R extracellular

domain). Hybridoma cell lines derived from such immunized mice, wherein the hybridoma secretes a monoclonal antibody that binds IGF-1R, also are provided herein.

Although human, partially human, or humanized antibodies will be suitable for many applications, particularly those involving administration of the antibody to a human subject, other types of antigen binding proteins will be suitable for certain applications. The non-human antibodies of the invention can be, for example, derived from any antibody-producing animal, such as mouse, rat, rabbit, goat, donkey, or non-human primate (such as monkey (*e.g.*, cynomologous or rhesus monkey) or ape (*e.g.*, chimpanzee)). Non-human antibodies of the invention can be used, for example, in *in vitro* and cell-culture based applications, or any other application where an immune response to the antibody of the invention does not occur, is insignificant, can be prevented, is not a concern, or is desired. In one embodiment, a non-human antibody of the invention is administered to a non-human subject. In another embodiment, the non-human antibody does not elicit an immune response in the non-human subject. In another embodiment, the non-human antibody is from the same species as the non-human subject, *e.g.*, a mouse antibody of the invention is administered to a mouse. An antibody from a particular species can be made by, for example, immunizing an animal of that species with the desired immunogen (*e.g.*, a soluble IGF-1R polypeptide) or using an artificial system for generating antibodies of that species (*e.g.*, a bacterial or phage display-based system for generating antibodies of a particular species), or by converting an antibody from one species into an antibody from another species by replacing, *e.g.*, the constant region of the antibody with a constant region from the other species, or by replacing one or more amino acid residues of the antibody so that it more closely resembles the sequence of an antibody from the other species. In one embodiment, the antibody is a chimeric antibody comprising amino acid sequences derived from antibodies from two or more different species.

Antigen binding proteins may be prepared by any of a number of conventional techniques. For example, they may be purified from cells that naturally express them (*e.g.*, an antibody can be purified from a hybridoma that produces it), or produced in recombinant expression systems, using any technique known in the art. See, for example, *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Kennet *et al.* (eds.), Plenum Press, New York (1980); and *Antibodies: A Laboratory Manual*, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1988).

Any expression system known in the art can be used to make the recombinant polypeptides of the invention. In general, host cells are transformed with a recombinant expression vector that comprises DNA encoding a desired polypeptide. Among the host cells that may be employed are prokaryotes, yeast or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or bacilli. Higher eukaryotic cells include insect cells and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman *et al.*, 1981, Cell 23:175), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, BHK (ATCC CRL 10) cell lines, and the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) as described by McMahan *et al.*, 1991, EMBO J. 10: 2821. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels *et al.* (*Cloning Vectors: A Laboratory Manual*, Elsevier, New York, 1985).



The transformed cells can be cultured under conditions that promote expression of the polypeptide, and the polypeptide recovered by conventional protein purification procedures. One such purification procedure includes the use of affinity chromatography, *e.g.*, over a matrix having all or a portion (*e.g.*, the extracellular domain) of IGF-1R bound thereto. Polypeptides contemplated for use herein include

5 substantially homogeneous recombinant mammalian anti-IGF-1R antibody polypeptides substantially free of contaminating endogenous materials.

Antigen binding proteins may be prepared, and screened for desired properties, by any of a number of known techniques. Certain of the techniques involve isolating a nucleic acid encoding a polypeptide chain (or portion thereof) of an antigen binding protein of interest (*e.g.*, an anti-IGF-1R antibody), and

10 manipulating the nucleic acid through recombinant DNA technology. The nucleic acid may be fused to another nucleic acid of interest, or altered (*e.g.*, by mutagenesis or other conventional techniques) to add, delete, or substitute one or more amino acid residues, for example.

In one aspect, the present invention provides antigen-binding fragments of an anti-IGF-1R antibody of the invention. Such fragments can consist entirely of antibody-derived sequences or can

15 comprise additional sequences. Examples of antigen-binding fragments include Fab, F(ab')<sub>2</sub>, single chain antibodies, diabodies, triabodies, tetrabodies, and domain antibodies. Other examples are provided in Lunde *et al.*, 2002, *Biochem. Soc. Trans.* 30:500-06.

Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain.

20 Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (V<sub>L</sub> and V<sub>H</sub>). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (*e.g.*, dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt *et al.*, 1997, *Prot. Eng.* 10:423; Kortt *et al.*, 2001, *Biomol. Eng.* 18:95-108). By combining different V<sub>L</sub> and V<sub>H</sub>-

25 comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum *et al.*, 2001, *Biomol. Eng.* 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Patent No. 4,946,778; Bird, 1988, *Science* 242:423; Huston *et al.*, 1988, *Proc. Natl. Acad. Sci. USA* 85:5879; Ward *et al.*, 1989, *Nature* 334:544; de Graaf *et al.*, 2002, *Methods Mol Biol.* 178:379-87. Single chain antibodies derived from antibodies provided herein include, but are not limited

30 to, scFvs comprising the variable domain combinations L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52) are encompassed by the present invention.

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Antigen binding proteins (*e.g.*, antibodies, antibody fragments, and antibody derivatives) of the invention can comprise any constant region known in the art. The light chain constant region can be, for example, a kappa- or lambda-type light chain constant region, *e.g.*, a human kappa- or lambda-type light chain constant region. The heavy chain constant region can be, for example, an alpha-, delta-, epsilon-,

40 gamma-, or mu-type heavy chain constant regions, *e.g.*, a human alpha-, delta-, epsilon-, gamma-, or mu-

type heavy chain constant region. In one embodiment, the light or heavy chain constant region is a fragment, derivative, variant, or mutein of a naturally occurring constant region.

Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, *i.e.*, subclass switching. Thus, IgG antibodies may be derived from an IgM antibody, for example, and *vice versa*. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, *e.g.*, DNA encoding the constant domain of an antibody of the desired isotype. See also Lantto *et al.*, 2002, *Methods Mol. Biol.* 178:303-16.

In one embodiment, an antigen binding protein of the invention comprises the IgG1 heavy chain domain of Figure 13 or a fragment of the IgG1 heavy chain domain of Figure 13. In another embodiment, an antigen binding protein of the invention comprises the kappa light chain constant chain region of Figure 13 or a fragment of the kappa light chain constant region of Figure 13. In another embodiment, an antigen binding protein of the invention comprises both the IgG1 heavy chain domain, or a fragment thereof, of Figure 13 and the kappa light chain domain, or a fragment thereof, of Figure 13.

Accordingly, the antigen binding proteins of the present invention include those comprising, for example, the variable domain combinations L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52, having a desired isotype (for example, IgA, IgG1, IgG2, IgG3, IgG4, IgM, IgE, and IgD) as well as Fab or F(ab')<sub>2</sub> fragments thereof. Moreover, if an IgG4 is desired, it may also be desired to introduce a point mutation (CPSCP → CPPCP) in the hinge region as described in Bloom *et al.*, 1997, *Protein Science* 6:407, incorporated by reference herein) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

Moreover, techniques for deriving antigen binding proteins having different properties (*i.e.*, varying affinities for the antigen to which they bind) are also known. One such technique, referred to as chain shuffling, involves displaying immunoglobulin variable domain gene repertoires on the surface of filamentous bacteriophage, often referred to as phage display. Chain shuffling has been used to prepare high affinity antibodies to the hapten 2-phenyloxazol-5-one, as described by Marks *et al.*, 1992, *BioTechnology*, 10:779.

In particular embodiments, antigen binding proteins of the present invention have a binding affinity ( $K_a$ ) for IGF-1R of at least  $10^6$ , measured as described in the Examples. In other embodiments, the antigen binding proteins exhibit a  $K_a$  of at least  $10^7$ , at least  $10^8$ , at least  $10^9$ , or at least  $10^{10}$ .

In another embodiment, the present invention provides an antigen binding protein that has a low dissociation rate from IGF-1R. In one embodiment, the antigen binding protein has a  $K_{off}$  of  $1 \times 10^{-4} \text{ s}^{-1}$  or lower. In another embodiment, the  $K_{off}$  is  $5 \times 10^{-5} \text{ s}^{-1}$  or lower. In another embodiment, the  $K_{off}$  is substantially the same as an antibody having a combination of light chain and heavy chain variable domain

sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the antigen binding protein binds to IGF-1R with substantially the same  $K_{off}$  as an antibody that comprises one or more CDRs from an antibody having a combination of light chain and heavy chain variable domain sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the antigen binding protein binds to IGF-1R with substantially the same  $K_{off}$  as an antibody that comprises one of the amino acid sequences illustrated in Figures 2 through 9. In another embodiment, the antigen binding protein binds to IGF-1R with substantially the same  $K_{off}$  as an antibody that comprises one or more CDRs from an antibody that comprises one of the amino acid sequences illustrated in Figures 2 through 9.

In another aspect, the present invention provides an antigen binding protein that binds to the L2 domain of human IGF-1R. Antigen binding proteins that bind to the L2 domain can be made using any technique known in the art. For example, such antigen binding proteins can be isolated using the full-length IGF-1R polypeptide (e.g., in a membrane-bound preparation), a soluble extracellular domain fragment of IGF-1R (an example of which is provided in Example 1), or a smaller fragment of the IGF-1R extracellular domain comprising or consisting of the L2 domain (examples of which are provided in Example 10). Antigen binding proteins so isolated can be screened to determine their binding specificity using any method known in the art (an example of which is provided in Example 10).

In another aspect, the present invention provides an antigen binding protein that binds to human IGF-1R expressed on the surface of a cell and, when so bound, inhibits IGF-1R signaling activity in the cell without causing a significant reduction in the amount of IGF-1R on the surface of the cell. Any method for determining or estimating the amount of IGF-1R on the surface and/or in the interior of the cell can be used. In one embodiment, the present invention provides an antigen binding protein that binds to the L2 domain of a human IGF-1R expressed on the surface of a cell and, when so bound, inhibits IGF-1R signaling activity in the cell without significantly increasing the rate of internalization of the IGF-1R from the surface of the cell. In other embodiments, binding of the antigen binding protein to the IGF-1R-expressing cell causes less than about 75%, 50%, 40%, 30%, 20%, 15%, 10%, 5%, 1%, or 0.1% of the cell-surface IGF-1R to be internalized. In another aspect, binding of the antigen binding protein to the IGF-1R-expressing cell causes a gradual reduction in the amount of IGF-1R on the cell surface such that within a few hours of contacting the cell with the antigen binding protein, little or no decrease in cell surface IGF-1R is detected, but, after several days or weeks of exposure of the cell to the antigen binding protein, a marked decrease in cell surface IGF-1R is detected.

In another aspect, the present invention provides an antigen binding protein having a half-life of at least one day *in vitro* or *in vivo* (e.g., when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antigen binding protein has a half-life of four days or longer. In another embodiment, the antigen binding protein has a half-life of eight days or longer. In another embodiment, the antigen binding protein is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antigen binding protein. In another embodiment, the antigen binding protein contains one or more point mutations to increase serum half life, such as described in WO 00/09560, published Feb.24, 2000, incorporated by reference.

The present invention further provides multi-specific antigen binding proteins, for example, bispecific antigen binding protein, e.g., antigen binding protein that bind to two different epitopes of IGF-1R, or to an epitope of IGF-1R and an epitope of another molecule, via two different antigen binding sites or regions. Moreover, bispecific antigen binding protein as disclosed herein can comprise an IGF-1R binding site from one of the herein-described antibodies and a second IGF-1R binding region from another of the herein-described antibodies, including those described herein by reference to other publications. Alternatively, a bispecific antigen binding protein may comprise an antigen binding site from one of the herein described antibodies and a second antigen binding site from another IGF-1R antibody that is known in the art, or from an antibody that is prepared by known methods or the methods described herein.

Numerous methods of preparing bispecific antibodies are known in the art, and discussed in US Patent Application 09/839,632, filed April 20, 2001 (incorporated by reference herein). Such methods include the use of hybrid-hybridomas as described by Milstein *et al.*, 1983, Nature 305:537, and others (U.S. Patent 4,474,893, U.S. Patent 6,106,833), and chemical coupling of antibody fragments (Brennan *et al.*, 1985, Science 229:81; Glennie *et al.*, 1987, J. Immunol. 139:2367; U.S. Patent 6,010,902). Moreover, bispecific antibodies can be produced via recombinant means, for example by using leucine zipper moieties (*i.e.*, from the Fos and Jun proteins, which preferentially form heterodimers; Kostelny *et al.*, 1992, J. Immunol. 148:1547) or other lock and key interactive domain structures as described in U.S. Patent 5,582,996. Additional useful techniques include those described in Kort *et al.*, 1997, *supra*; U.S. Patent 5,959,083; and U.S. Patent 5,807,706.

In another aspect, the antigen binding protein of the present invention comprises a derivative of an antibody. The derivatized antibody can comprise any molecule or substance that imparts a desired property to the antibody, such as increased half-life in a particular use. The derivatized antibody can comprise, for example, a detectable (or labeling) moiety (e.g., a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodense (e.g., gold) bead), or a molecule that binds to another molecule (e.g., biotin or streptavidin)), a therapeutic or diagnostic moiety (e.g., a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antibody for a particular use (e.g., administration to a subject, such as a human subject, or other *in vivo* or *in vitro* uses). Examples of molecules that can be used to derivatize an antibody include albumin (e.g., human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antibodies can be prepared using techniques well known in the art. In one embodiment, the antibody is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically

modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyrrolidone), polyethylene glycols, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols. US Pat. App. No. 20030195154.

In another aspect, the present invention provides methods of screening for a molecule that binds to IGF-1R using the antigen binding proteins of the present invention. Any suitable screening technique can be used. In one embodiment, an IGF-1R molecule, or a fragment thereof to which an antigen binding protein of the present invention binds, is contacted with the antigen binding protein of the invention and with another molecule, wherein the other molecule binds to IGF-1R if it reduces the binding of the antigen binding protein to IGF-1R. Binding of the antigen binding protein can be detected using any suitable method, e.g., an ELISA. Detection of binding of the antigen binding protein to IGF-1R can be simplified by detectably labeling the antigen binding protein, as discussed above. In another embodiment, the IGF-1R-binding molecule is further analyzed to determine whether it inhibits IGF-1R, IGF-1, and/or IGF-2-mediated signaling.

#### 15 Nucleic acids

In one aspect, the present invention provides isolated nucleic acid molecules. The nucleic acids comprise, for example, polynucleotides that encode all or part of an antigen binding protein, for example, one or both chains of an antibody of the invention, or a fragment, derivative, mutein, or variant thereof, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide, anti-sense nucleic acids for inhibiting expression of a polynucleotide, and complementary sequences of the foregoing. The nucleic acids can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleotides in length, and/or can comprise one or more additional sequences, for example, regulatory sequences, and/or be part of a larger nucleic acid, for example, a vector. The nucleic acids can be single-stranded or double-stranded and can comprise RNA and/or DNA nucleotides, and artificial variants thereof (e.g., peptide nucleic acids).

Nucleic acids encoding antibody polypeptides (e.g., heavy or light chain, variable domain only, or full length) may be isolated from B-cells of mice that have been immunized with IGF-1R. The nucleic acid may be isolated by conventional procedures such as polymerase chain reaction (PCR).

Figure 1 provides nucleic acid sequences encoding the variable regions of the heavy and light chain variable regions shown in Figures 2 and 3. The skilled artisan will appreciate that, due to the degeneracy of the genetic code, each of the polypeptide sequences in Figures 2 through 9 also is encoded by a large number of other nucleic acid sequences. The present invention provides each degenerate nucleotide sequence encoding each antigen binding protein of the invention.

The invention further provides nucleic acids that hybridize to other nucleic acids (e.g., nucleic acids comprising a nucleotide sequence of Figure 1) under particular hybridization conditions. Methods for hybridizing nucleic acids are well-known in the art. See, e.g., Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. As defined herein, a moderately stringent hybridization condition uses a prewashing solution containing 5X sodium chloride/sodium citrate (SSC), 0.5% SDS, 1.0 mM EDTA

(pH 8.0), hybridization buffer of about 50% formamide, 6X SSC, and a hybridization temperature of 55° C (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42° C), and washing conditions of 60° C, in 0.5X SSC, 0.1% SDS. A stringent hybridization condition hybridizes in 6X SSC at 45° C, followed by one or more washes in 0.1X SSC, 0.2% SDS at 68° C. Furthermore, one of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that nucleic acids comprising nucleotide sequences that are at least 65, 70, 75, 80, 85, 90, 95, 98 or 99% identical to each other typically remain hybridized to each other. The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are set forth by, for example, Sambrook, Fritsch, and Maniatis (1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11; and *Current Protocols in Molecular Biology*, 1995, Ausubel *et al.*, eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4), and can be readily determined by those having ordinary skill in the art based on, for example, the length and/or base composition of the DNA.

Changes can be introduced by mutation into a nucleic acid, thereby leading to changes in the amino acid sequence of a polypeptide (*e.g.*, an antigen binding protein) that it encodes. Mutations can be introduced using any technique known in the art. In one embodiment, one or more particular amino acid residues are changed using, for example, a site-directed mutagenesis protocol. In another embodiment, one or more randomly selected residues is changed using, for example, a random mutagenesis protocol. However it is made, a mutant polypeptide can be expressed and screened for a desired property (*e.g.*, binding to IGF-1R or blocking the binding of IGF-1 and/or IGF-2 to IGF-1R).

Mutations can be introduced into a nucleic acid without significantly altering the biological activity of a polypeptide that it encodes. For example, one can make nucleotide substitutions leading to amino acid substitutions at non-essential amino acid residues. In one embodiment, a nucleotide sequence provided in Figure 1, or a desired fragment, variant, or derivative thereof, is mutated such that it encodes an amino acid sequence comprising one or more deletions or substitutions of amino acid residues that are shown in Figures 2 through 9 to be residues where two or more sequences differ. In another embodiment, the mutagenesis inserts an amino acid adjacent to one or more amino acid residues shown in Figures 2 through 9 to be residues where two or more sequences differ. Alternatively, one or more mutations can be introduced into a nucleic acid that selectively change the biological activity (*e.g.*, binding of IGF-1R, inhibiting IGF-1 and/or IGF-2, *etc.*) of a polypeptide that it encodes. For example, the mutation can quantitatively or qualitatively change the biological activity. Examples of quantitative changes include increasing, reducing or eliminating the activity. Examples of qualitative changes include changing the antigen specificity of an antigen binding protein.

In another aspect, the present invention provides nucleic acid molecules that are suitable for use as primers or hybridization probes for the detection of nucleic acid sequences of the invention. A nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding a full-length polypeptide of the invention, for example, a fragment that can be used as a probe or primer or a fragment encoding an active portion (*e.g.*, an IGF-1R binding portion) of a polypeptide of the invention.

Probes based on the sequence of a nucleic acid of the invention can be used to detect the nucleic acid or similar nucleic acids, for example, transcripts encoding a polypeptide of the invention. The probe

can comprise a label group, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used to identify a cell that expresses the polypeptide.

5 In another aspect, the present invention provides vectors comprising a nucleic acid encoding a polypeptide of the invention or a portion thereof. Examples of vectors include, but are not limited to, plasmids, viral vectors, non-episomal mammalian vectors and expression vectors, for example, recombinant expression vectors.

10 The recombinant expression vectors of the invention can comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. The recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cells (*e.g.*, SV40 early gene enhancer, Rous sarcoma virus promoter and cytomegalovirus promoter), those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences, see Voss *et al.*, 1986, Trends Biochem. Sci. 11:287, Maniatis *et al.*, 1987, Science 236:1237, incorporated by reference  
15 herein in their entireties), and those that direct inducible expression of a nucleotide sequence in response to particular treatment or condition (*e.g.*, the metallothionin promoter in mammalian cells and the tet-responsive and/or streptomycin responsive promoter in both prokaryotic and eukaryotic systems (see *id.*). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, *etc.* The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

20 In another aspect, the present invention provides host cells into which a recombinant expression vector of the invention has been introduced. A host cell can be any prokaryotic cell (for example, *E. coli*) or eukaryotic cell (for example, yeast, insect, or mammalian cells (*e.g.*, CHO cells)). Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable  
25 markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die), among other methods.

#### Indications

35 In one aspect, the present invention provides methods of treating a subject. The method can, for example, have a generally salubrious effect on the subject, *e.g.*, it can increase the subject's expected longevity. Alternatively, the method can, for example, treat, prevent, cure, relieve, or ameliorate ("treat") a disease, disorder, condition, or illness ("a condition"). Among the conditions to be treated in accordance with the present invention are conditions characterized by inappropriate expression or activity of IGF-1, IGF-2, and/or IGF-1R. In some such conditions, the expression or activity level is too high, and the  
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treatment comprises administering an IGF-1R antagonist as described herein. In other such conditions, the expression or activity level is too low, and the treatment comprises administering an IGF-1R agonist as described herein.

One example of a type of condition that can be treated using the methods and compositions of the present invention is a condition that involves cell growth, for example, a cancerous condition. Thus, in one embodiment, the present invention provides compositions and methods for treating a cancerous condition. The cancerous condition can be any cancerous condition that can be treated using the compositions comprised herein, for example, IGF-1R antagonizing antigen binding proteins such as anti-IGF-1R antibodies, antibody fragments, or antibody derivatives. Examples of cancerous conditions include, for example, Acute Lymphoblastic Leukemia, Adrenocortical Carcinoma, AIDS-Related Cancers, AIDS-Related Lymphoma, Anal Cancer, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Basal Cell Carcinoma, Extrahepatic Bile Duct Cancer, Bladder Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma Bone Cancer, Brain Tumors (e.g., Brain Stem Glioma, Cerebellar Astrocytoma, Cerebral Astrocytoma/Malignant Glioma, Ependymoma, Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumors, Visual Pathway and Hypothalamic Glioma), Breast Cancer, Bronchial Adenomas/Carcinoids, Burkitt's Lymphoma, Carcinoid Tumor, Gastrointestinal Carcinoid Tumor, Carcinoma of Unknown Primary, Primary Central Nervous System, Cerebellar Astrocytoma, Cerebral Astrocytoma/Malignant Glioma, Cervical Cancer, Childhood Cancers, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Chronic Myeloproliferative Disorders, Colon Cancer, Colorectal Cancer, Cutaneous T-Cell Lymphoma, Endometrial Cancer, Ependymoma, Esophageal Cancer, Ewing's Family of Tumors, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Intraocular Melanoma Eye Cancer, Retinoblastoma Eye Cancer, Gallbladder Cancer, Gastric (Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Germ Cell Tumors (e.g., Extracranial, Extragonadal, and Ovarian), Gestational Trophoblastic Tumor, Glioma (e.g., Adult, Childhood Brain Stem, Childhood Cerebral Astrocytoma, Childhood Visual Pathway and Hypothalamic), Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular (Liver) Cancer, Hodgkin's Lymphoma, Hypopharyngeal Cancer, Hypothalamic and Visual Pathway Glioma, Intraocular Melanoma, Islet Cell Carcinoma (Endocrine Pancreas), Kaposi's Sarcoma, Kidney (Renal Cell) Cancer, Laryngeal Cancer, Leukemia (e.g., Acute Lymphoblastic, Acute Myeloid, Chronic Lymphocytic, Chronic Myelogenous, and Hairy Cell), Lip and Oral Cavity Cancer, Liver Cancer, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Lymphoma (e.g., AIDS-Related, Burkitt's, Cutaneous T-Cell, Hodgkin's, Non-Hodgkin's, and Primary Central Nervous System), Waldenström's Macroglobulinemia, Malignant Fibrous Histiocytoma of Bone/Osteosarcoma, Medulloblastoma, Melanoma, Intraocular (Eye) Melanoma, Merkel Cell Carcinoma, Mesothelioma, Metastatic Squamous Neck Cancer with Occult Primary, Multiple Endocrine Neoplasia Syndrome, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Diseases, Myelogenous Leukemia, Chronic Myeloid Leukemia, Multiple Myeloma, Chronic Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Oral Cancer, Oropharyngeal Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Islet Cell Pancreatic Cancer, Paranasal Sinus



and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pineoblastoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Primary Central Nervous System Lymphoma, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Soft Tissue  
 5 Sarcoma, Uterine Sarcoma, Sezary Syndrome, non-Melanoma Skin Cancer, Merkel Cell Skin Carcinoma, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Cutaneous T-Cell Lymphoma, Testicular Cancer, Thymoma, Thymic Carcinoma, Thyroid Cancer, Gestational Trophoblastic Tumor, Carcinoma of Unknown Primary Site, Cancer of Unknown Primary Site, Urethral Cancer, Endometrial  
 10 Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenström's Macroglobulinemia, and Wilms' Tumor.

Four different groups have studied a total of 425 breast cancers, mostly ductal in origin, and 48 normal tissues or benign specimens by radioimmunoassay ("RIA") or immunohistochemistry ("IHC") (Papa *et al.*, 1993, Cancer Research 53: 3736-40, Happerfield *et al.*, 1997, Journal of Pathology 183: 412-17; Ellis *et al.*, 1998, Breast Cancer Research & Treatment 52: 175-84, Lee *et al.*, 1998, Breast Cancer  
 15 Research & Treatment 47: 295-302, Schnarr *et al.*, 2000, International Journal of Cancer 89: 506-13). These studies suggest that elevated IGF-1R expression, on the order of 5-10 fold, is associated with favorable prognosis and biomarkers (ER+ PR+), suggesting that estrogen and IGF cooperate in the maintenance or progression of well differentiated tumor. Similarly, estrogen has been shown to be essential for the growth and survival of the ER+ MCF-7 breast cancer cell line, and in this context IGF-1R is up-  
 20 regulated by estrogen treatment (reviewed in Ellis *et al.*, 1998, Breast Cancer Research & Treatment 52: 175-84). Thus, in one embodiment, the present invention provides a method of treating breast cancer in a subject in need of such treatment, comprising administering to the subject an effective amount of an IGF-1R antagonist as described herein. In another embodiment, the method further comprises administering a hormone inhibitor, e.g., an estrogen inhibitor.

A retrospective IGF-1R IHC analysis has been reported for a collection of 12 colonic adenomas, 36 primary colorectal adenocarcinomas and 27 corresponding metastases, and 34 adjacent normal tissues (Hakam *et al.*, 1999, Human Pathology. 30: 1128-33). The frequency of moderate to strong IHC staining appeared to dramatically increase with higher stage and tumor grade (0% normal vs. 93 % metastases). The results are consistent with RNA analysis by RNase protection assay ("RPA") (Freier *et al.*, 1999, Gut 44:  
 30 704-08). Thus, in one embodiment, the present invention provides a method of treating colon cancer in a subject in need of such treatment, comprising administering to the subject an effective amount of an IGF-1R antagonist as described herein.

High plasma IGF-1 and reduced IGFbp3 in men 40-80 years old is associated with increased prostate cancer risk (Chan *et al.*, 1998, Science 279: 563-6). High IGF-1 is associated with a risk of other  
 35 cancers including breast (Hankinson *et al.*, 1998, Lancet 351: 1393-96), colon (Ma *et al.*, 1999, Journal of the National Cancer Institute 91: 620-25) and lung (Yu *et al.*, 1999, Journal of the National Cancer Institute 91: 151-56). In transgenic mouse models, tumor incidence is increased by IGF-1 overexpression in diverse locations (Bol *et al.*, 1997, Oncogene 14: 1725-34; DiGiovanni *et al.*, 2000, Cancer Research 60: 1561-70; DiGiovanni *et al.*, 2000, Proceedings of the National Academy of Sciences of the United States of America  
 40 97: 3455-60, Hadsell *et al.*, 2000, Oncogene 19: 889-98). These mouse studies point to a role for both

serum and stromal produced IGF-1. Thus, in one embodiment, the present invention provides a method of treating a subject in need of such treatment, comprising administering to the subject an effective amount of an antagonist of IGF-1R as described herein, wherein the antagonist inhibits the activation of IGF-1R by IGF-1. In another embodiment, the subject has cancer. In another embodiment, the subject has a tumor. In another embodiment, the cancer is prostate, breast, colon or lung cancer.

It has been observed that bone is the major source of IGF-1 in the body. Thus, in one aspect, the present invention provides compositions and methods for inhibiting IGF-1R in a bone of a subject. In one embodiment, an IGF-1R inhibitor of the present invention is administered to a subject that has, or is at risk for developing, a tumor in a bone. The tumor can be, for example, a primary tumor or a metastatic tumor. The treatment optionally further comprises administering to the subject one or more additional therapeutic and/or palliative treatments, for example, an anti-tumor treatment (e.g., chemotherapy, radiation therapy, or anti-hormone therapy) or a treatment that inhibits bone turnover (e.g., denosumab (Amgen Inc., Thousand Oaks, CA)).

IGF-2 is overexpressed in a variety of tumors and stromal tissues. IGF-2 levels appear especially high (as much as 40 fold) in primary liver cancers (Cariani *et al.*, 1988, Cancer Research 48: 6844-49) and adenocarcinoma of the colon (Freier *et al.*, 1999, Gut 44: 704-08). Many of the overgrowth disorders are associated with an increased incidence of childhood tumors. Five to ten percent of individuals with either the prenatal growth disorder Beckwith-Weidmann Syndrome (BWS) or hemihyperplasia develop tumors such as nephroblastoma, adrenal carcinoma, and neuroblastoma (reviewed by Morison *et al.*, 1998, Molecular Medicine Today 4: 110-05). The tumor-predisposing factor in these children appears to be the mosaic loss of maternal IGF-2 gene imprinting, or duplication of the paternal chromosomal arm (11p) that carries IGF-2. Both alterations would increase the level of IGF-2 expression. IGF-2 overexpression as a result of mosaic uniparental disomy or loss of IGF-2 imprinting has also been detected in Wilms tumors. Growth disorders are not observed in these children even though the IGF-2 gene alterations also occur in some normal tissues, perhaps reflecting the tissue distribution of the affected cells. Imprinting of the maternal IGF-2 gene also occurs in mice, and the effects of IGF-2 overexpression are consistent with the human situation (Cariani *et al.*, 1991, Journal of Hepatology 13: 220-26, Schirmacher *et al.*, 1992, Cancer Research 52: 2549-56; Harris *et al.*, 1998, Oncogene 16: 203-09). The incidence of tumors and organomegaly increases in mice that transgenically express excess IGF-2 (Christofori *et al.*, 1994, Nature 369: 414-18, Ward *et al.*, 1994, Proceedings of the National Academy of Sciences of the United States of America 91: 10365-9, Wolf *et al.*, 1994, Endocrinology 135: 1877-86, Bates *et al.*, 1995, British Journal of Cancer 72: 1189-93, Hassan *et al.*, 2000, Cancer Research 60: 1070-76). Local IGF-2 overexpression increases the spontaneous appearance of prostate, mammary, intestinal, liver and epidermal tumors. Plasma specific expression using liver promoters elevate hepatocellular carcinomas and lymphoma. Thus, in one embodiment, the present invention provides a method of treating a subject in need of such treatment, comprising administering to the subject an effective amount of an antagonist of IGF-1R as described herein, wherein the antagonist inhibits the activation of IGF-1R by IGF-2. In another embodiment, the subject has cancer. In another embodiment, the subject has a tumor. In another embodiment, the subject has liver cancer, adenocarcinoma of the colon, Beckwith-Weidmann Syndrome, hemihyperplasia, nephroblastoma, adrenal carcinoma, neuroblastoma, mosaic loss of maternal IGF-2 gene imprinting, duplication of the

paternal chromosomal arm (11p), increased IGF-2 expression, a tumor (*e.g.*, a prostate, mammary, intestinal, liver, epidermal, or Wilms tumor), organomegaly, hepatocellular carcinoma, or lymphoma.

In another aspect, the invention provides methods of preventing or inhibiting a cancer from spreading to another part of the body, or of treating a cancer that has spread to another part of the body. In one embodiment, the cancer has spread to a regional lymph node. In another embodiment, the cancer is metastatic. The primary tumor can be any kind of tumor, for example, an adenocarcinoma tumor (*e.g.*, a prostate adenocarcinoma tumor, a breast carcinoma tumor, or a renal cell carcinoma tumor), a non-small cell or small cell lung cancer tumor, a thyroid cancer tumor, *etc.* The site of the metastatic tumor can be anywhere in the body. It can be, for example, in bone, the lymph system, lung, brain, eye, skin, pancreas, or liver. In one particular embodiment, a subject having a tumor disease is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that the primary tumor is prevented from metastasizing. In another particular embodiment, a subject having a primary tumor is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that the primary tumor is inhibited from metastasizing. In another particular embodiment, a subject having a metastatic tumor is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that growth or spreading of the secondary tumor is inhibited. In another particular embodiment, a subject having a metastatic tumor is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that the secondary tumor is reduced in size. In a more particular embodiment, the primary tumor is an adenocarcinoma tumor, a non-small cell lung tumor, a small cell lung tumor, or a thyroid cancer. In another more particular embodiment, the metastatic tumor is in a bone. In another more particular embodiment, a metastatic tumor is prevented or inhibited from forming in a bone. In another more particularly defined embodiment, the method comprises treating the subject with an IGF-1R inhibiting composition of the present invention and one or more other treatments (*e.g.*, a treatment that kills or inhibits the growth of cancer cells, such as radiation, hormonal therapy, or chemotherapy, or a treatment that inhibits the turnover of bone, such as denosumab), non-limiting examples of which are provided herein. The one or more other treatments can include, for example the standard of care for the subject's particular condition and/or palliative care.

Without being bound to any particular theory, tumor cells appear to depend on the PI3 Kinase/Akt signaling pathway to resist the apoptosis-inducing activity of chemotherapeutics, radiation, and anti-hormone therapy. Thus, in one embodiment, the present invention provides methods of treating a subject in need of such treatment comprising administering to the subject an IGF-1R antagonist of the present invention and a chemotherapeutic, radiation, and/or an anti-hormone therapy. This concept has been validated experimentally in cell culture models and rodent tumor models by antisense and dominant negative mutations (reviewed by Baserga *et al.*, 1997, *Biochimica et Biophysica Acta* 1332: F105-26, Baserga, 2000, *Oncogene* 19: 5574-81). In one embodiment, the chemotherapeutic agents is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, anti-survival agents, biological response modifiers, anti-hormones, *e.g.* anti-androgens, and anti-angiogenesis agents.

One example of a chemotherapeutic agent that can be administered in combination with an IGF-1 receptor inhibitor of the invention is CPT-11. CPT-11 (Irinotecan hydrochloride trihydrate) is a semi

synthetic, water soluble derivative of camptothecin, a plant alkaloid. CPT-11 and an associated metabolite called SN38 inhibit topoisomerase 1 (TOPO1). This enzyme introduces reversible single-strand breaks in DNA that allow unwinding and permit DNA replication to proceed. Inhibition of TOPO1 prevents religation of single-strand breaks after DNA replication resulting in greatly increased chromosomal fragmentation. This DNA damage promotes cell death by apoptosis through the action of p53 and other systems that monitor genome integrity. The cytotoxic effect of CPT-11 is generally limited to cells that are replicating DNA (S-Phase). Quiescent cells are largely unaffected.

In another embodiment, the present invention provides treating a subject in need thereof with an effective amount of an IGF-1R antagonist of the present invention and with an effective amount of an apoptosis-inducing agent.

In another embodiment, an anti-angiogenesis agent, such as an MMP-2 (matrix-metalloproteinase 2) inhibitor, an MMP-9 (matrix-metalloproteinase 9) inhibitor, and/or a COX-II (cyclooxygenase II) inhibitor, is used in conjunction with a compound of the invention. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), BEXTRA™ (valdecoxib), and VIOXX™ (rofecoxib). Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published Oct. 24, 1996), WO 96/27583 (published Mar. 7, 1996), European Patent Application No. 97304971.1 (filed Jul. 8, 1997), European Patent Application No. 99308617.2 (filed Oct. 29, 1999), WO 98/07697 (published Feb. 26, 1998), WO 98/03516 (published Jan. 29, 1998), WO 98/34918 (published Aug. 13, 1998), WO 98/34915 (published Aug. 13, 1998), WO 98/33768 (published Aug. 6, 1998), WO 98/30566 (published Jul. 16, 1998), European Patent Publication 606,046 (published Jul. 13, 1994), European Patent Publication 931,788 (published Jul. 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published Oct. 21, 1999), WO 99/52889 (published Oct. 21, 1999), WO 99/29667 (published Jun. 17, 1999), PCT International Application No. PCT/IB98/01113 (filed Jul. 21, 1998), European Patent Application No. 99302232.1 (filed Mar. 25, 1999), Great Britain patent application number 9912961.1 (filed Jun. 3, 1999), U.S. Provisional Application No. 60/148,464 (filed Aug. 12, 1999), U.S. Pat. No. 5,863,949 (issued Jan. 26, 1999), U.S. Pat. No. 5,861,510 (issued Jan. 19, 1999), and European Patent Publication 780,386 (published Jun. 25, 1997), all of which are incorporated herein in their entireties by reference. In one embodiment, the MMP inhibitor is one that does not demonstrate arthralgia. In another embodiment, the MMP inhibitor selectively inhibits MMP-2 and/or MMP-9 relative to other matrix-metalloproteinases (*i.e.*, MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list: 3-[[4-(4-fluoro-phenoxy)-benzene-sulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4-fluoro-benzoyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; (R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzoyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-pi-

peridine-2-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro--pyran-4-yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and (R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide; and pharmaceutically acceptable salts, solvates, derivatives, and other preparations of the compounds.

Sporadic mutations that inactivate the PTEN gene product occur relatively frequently in most human cancers (Yamada *et al.*, 2001, J Cell Sci 114:2375-82, Hill *et al.*, 2002, Pharmacol Therapeut 93:243-51). Loss of PTEN causes the Akt phosphorylated state to persist through loss of the ability to down-regulate stimulatory signals originating from IGF-1R and other sources. The status of the p53 tumor suppressor also influences the activity of the IGF-1R signaling system. In the ground state, the basal or constitutive transcription of IGF-1R is repressed by p53 via an indirect mechanism. Activation of Akt promotes the phosphorylation of mdm2, which then binds the p53 tumor suppressor and promotes its degradation (Mayo *et al.*, 2002, TIBS 27:462-67), resulting in increased IGF-1R expression. A similar outcome is observed when p53 is inactivated by mutation. When transiently expressed in Saos-2 (a human osteosarcoma cell line) and RD (a rhabdomyosarcoma cell line), wild-type p53 is able to suppress the activity of a cotransfected IGF-1R promoter construct, whereas tumor-derived, mutant versions of p53 have no effect. It has been proposed that the increased level of IGF-1R promotes the resistance to apoptosis associated with p53 loss in malignant cells (Werner *et al.*, 2000, Cell Mol Life Sci 57:932-42). Thus, in one embodiment, the present invention provides a method of treating a cancerous condition in a subject in need of such treatment comprising administering to the subject an effective amount of an IGF-1R antagonist as described herein, wherein the cancerous condition is characterized by cells that have a reduced expression or activity of p53.

The WT1 (Wilms kidney tumor suppressor 1 protein) also has been shown to bind and repress the IGF-1R promoter. Thus, in one embodiment, the present invention provides a method of treating a cancerous condition in a subject in need of such treatment comprising administering to the subject an effective amount of an IGF-1R antagonist as described herein wherein the cancerous condition is characterized by a reduced expression or activity of WT1.

The proliferation of normal fibroblasts has been shown to require, under defined culture conditions, the combined action of IGF and a stromal growth factor (*e.g.* PDGF, EGF) to ramp-up Ras/Raf/Map Kinase and promote cell cycle entry (the G0 to G1 transition). Fibroblasts derived from IGF-1R (-/-) mice do not respond to growth factor alone, or most oncogenes (*e.g.* oncogenic Ras) that activate the Ras/Raf/Map Kinase pathway. Thus, in one embodiment, the present invention provides a method of treating a subject in need of such treatment comprising administering to the subject an IGF-1R antagonist as described herein and an agent that targets a growth factor and/or a growth factor receptor, such as a growth factor receptor tyrosine kinase, *e.g.*, the EGFR, HER-2, bcr-abl, VEGFR, Kit, raf, mTOR, CDK1/2, VEGFR2, PKC $\beta$ , Mek, and/or KDR. Examples of molecules that target such growth factors and/or receptors include panitumumab (Abgenix, Fremont, CA/Amgen, Thousand Oaks, CA), HERCEPTIN<sup>TM</sup> (Genentech, South San Francisco, CA), GLEEVECT<sup>TM</sup> (Novartis, East Hanover, NJ), IRESSA<sup>TM</sup>

(AstraZeneca, Wilmington, DE), ERBITUX™, (ImClone, New York, NY), AVASTIN™, (Genentech), PTK787 (Novartis), SU11248 (Pfizer, New York, NY), TARCEVA™ (OSI Pharmaceuticals, Melville, NY), 43-9006 (Bayer, West Haven, CT), CCI-779 (Wyeth, Madison, NJ), RAD001 (Novartis), BMS-387032 (Bristol-Myers Squibb, New York, NY), IMC-1C11 (ImClone), LY333531 (Eli Lilly, Indianapolis, IN), PD 184352 (Pfizer), 2C4 (Genentech), and GW2016 (GlaxoSmithKline, Research Triangle Park, NC).

The role of IGF-1R in hematological malignancies has been reviewed by (Novak *et al.*, 2003, *Insulin-Like Growth Factors and Hematological Malignancies in Insulin-Like Growth Factors*, LeRoith *et al.*, ed.s, Landes Bioscience). A functional role for the IGF-1R in hematopoietic malignancies is demonstrated by, for example, the ability of IGF-1R monoclonal antibodies to block transformed cell growth in culture. IGF-I has been found to enhance growth of freshly isolated human acute myelogenous leukemia and acute lymphoblastic leukemia blasts. With respect to T cell malignancies, IGF-I has been shown to influence the growth of murine lymphoma cells bearing a pre-T cell phenotype and, immature and mature primary human T lineage acute lymphoblastic leukemia cells were found to express high numbers of IGF-1R. Thus, in one embodiment, the present invention provides methods of treating a hematological malignancy in a subject in need thereof comprising administering to the subject an antagonist of IGF-1R as described herein. In another embodiment, the malignancy is an acute myelogenous leukemia, an acute lymphoblastic leukemia, or a T cell malignancy.

In another aspect, the present invention provides methods of identifying subjects who are more likely to benefit from treatment using the compositions and/or methods of treatment of the present invention. Such methods can enable a caregiver to better tailor a therapeutic regimen to a particular subject's needs and reduce the likelihood of an ineffective or counterproductive course of treatment. In one embodiment, the present invention provides a method of determining whether a subject is a candidate for treatment using a composition or method as described herein comprising determining whether a target cell type in the subject expresses IGF-1R, wherein if the target cell type expresses IGF-1R, then the subject is a candidate for treatment. In another embodiment, the method comprises determining the approximate average number of IGF-1R molecules per target cell, wherein  $10^2$ ,  $10^3$ ,  $10^4$ ,  $10^5$ , or  $10^6$  IGF-1R per cell indicates that the subject is a candidate for treatment. The approximate average number of IGF-1R molecules per target cell can be determined using any technique known in the art, for example, by staining a sample comprising cells of the target cell type with an IGF-1R binding molecule, and detecting the amount of IGF-1R binding molecule bound to the sample, where the amount of IGF-1R binding molecule detected is proportional to the average number of IGF-1R molecules in the sample. In another embodiment, the method comprises comparing the approximate average number of IGF-1R molecules per target cell to a reference standard, wherein if the approximate average number of IGF-1R molecules per target cell is greater than the reference standard, then the subject is more likely to benefit from treatment using the compositions and/or methods of treatment of the present invention. In another embodiment, the target cell type is a cancerous cell type. In another embodiment, the target cell type is a colon cancer cell type, a breast cancer cell type, an NSCLC cell type, or a leukemic cell type.

In another embodiment, a subject who is a candidate for treatment is identified by detecting IGF-1 and/or IGF-2 in the target cell type, or in the stratum of the target cell type. In another embodiment, the

target cell type is a cancerous cell type. In another embodiment, the target cell type is a colon cancer cell type, a breast cancer cell type, an NSCLC cell type, or a leukemic cell type.

5 In another embodiment, a subject who is a candidate for treatment is identified by detecting activity of IGF-1R-mediated signaling in the target cell type, wherein IGF-1R-mediated signaling in the target cell type indicates that the subject is a candidate for treatment. Examples of molecules that can be monitored for IGF-1R-dependent changes are shown in Figure 10, such as molecules in the PI3/Akt pathway, *e.g.*, IGF-1R, IRS adapters, Akt, *etc.* Such molecules can be monitored for, for example, a change in phosphorylation status, *e.g.*, an increase in phosphorylation. Phosphospecific antibodies that recognize the activated forms of these protein markers are highly developed, and these reagents have proven to be reliable for immunoblot detection in experimental systems.

10 The compositions and/or methods of the present invention also can be used, for example, in cosmetic treatments, in veterinary treatments, to increase longevity, to treat reproductive defects, and to treat a variety of growth related disorders.

#### 15 Therapeutic methods and administration of antigen binding proteins

Certain methods provided herein comprise administering an IGF-1R binding antigen binding protein to a subject, thereby reducing an IGF-1-induced biological response that plays a role in a particular condition. In particular embodiments, methods of the invention involve contacting endogenous IGF-1R with an IGF-1R binding antigen binding protein, *e.g.*, via administration to a subject or in an *ex vivo* procedure.

20 The term "treatment" encompasses alleviation or prevention of at least one symptom or other aspect of a disorder, or reduction of disease severity, and the like. An antigen binding protein need not effect a complete cure, or eradicate every symptom or manifestation of a disease, to constitute a viable therapeutic agent. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur or worsen in a subject, is sufficient. One embodiment of the invention is directed to a method comprising administering to a patient an IGF-1R antagonist in an amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

25 As is understood in the pertinent field, pharmaceutical compositions comprising the molecules of the invention are administered to a subject in a manner appropriate to the indication. Pharmaceutical compositions may be administered by any suitable technique, including but not limited to parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes, by bolus injection, or continuous infusion. Localized administration, *e.g.* at a site of disease or injury is contemplated, as are transdermal delivery and sustained release from implants. Delivery by inhalation

includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments.

5 Use of antigen binding proteins in *ex vivo* procedures also is contemplated. For example, a patient's blood or other bodily fluid may be contacted with an antigen binding protein that binds IGF-1R *ex vivo*. The antigen binding protein may be bound to a suitable insoluble matrix or solid support material.

10 Advantageously, antigen binding proteins are administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents, for example, a second IGF-1 receptor-inhibiting substance, an anti-angiogenic substance, a chemotherapeutic substance, an analgesic substance, *etc.*, non-exclusive examples of which are provided herein. In various particular embodiments, the composition comprises one, two, three, four, five, or six physiologically active agents in addition to an IGF-1R binding antigen binding protein

15 In one embodiment, the pharmaceutical composition comprise an antigen binding protein of the invention together with one or more substances selected from the group consisting of a buffer, an antioxidant such as ascorbic acid, a low molecular weight polypeptide (such as those having fewer than 10 amino acids), a protein, an amino acid, a carbohydrate such as glucose, sucrose or dextrans, a chelating agent such as EDTA, glutathione, a stabilizer, and an excipient. Neutral buffered saline or saline mixed with conspecific serum albumin are examples of appropriate diluents. In accordance with appropriate industry standards, preservatives such as benzyl alcohol may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions (*e.g.*, sucrose) as diluents. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in Remington's Pharmaceutical Sciences, 16<sup>th</sup> Ed. (1980) and 20<sup>th</sup> Ed. (2000), Mack Publishing Company, Easton, PA.

25 Kits for use by medical practitioners include an IGF-1 receptor-inhibiting substance of the invention and a label or other instructions for use in treating any of the conditions discussed herein. In one embodiment, the kit includes a sterile preparation of one or more IGF-1R binding antigen binding proteins, which may be in the form of a composition as disclosed above, and may be in one or more vials.

30 Dosages and the frequency of administration may vary according to such factors as the route of administration, the particular antigen binding proteins employed, the nature and severity of the disease to be treated, whether the condition is acute or chronic, and the size and general condition of the subject. Appropriate dosages can be determined by procedures known in the pertinent art, *e.g.* in clinical trials that may involve dose escalation studies.

35 An IGF-1 receptor inhibiting substance of the invention may be administered, for example, once or more than once, *e.g.*, at regular intervals over a period of time. In particular embodiments, an antigen binding protein is administered over a period of at least a month or more, *e.g.*, for one, two, or three months or even indefinitely. For treating chronic conditions, long-term treatment is generally most effective. However, for treating acute conditions, administration for shorter periods, *e.g.* from one to six weeks, may be sufficient. In general, the antigen binding protein is administered until the patient manifests a medically relevant degree of improvement over baseline for the chosen indicator or indicators.

40



Particular embodiments of the present invention involve administering an antigen binding protein at a dosage of from about 1 ng of antigen binding protein per kg of subject's weight per day ("1ng/kg/day") to about 10 mg/kg/day, more preferably from about 500 ng/kg/day to about 5 mg/kg/day, and most preferably from about 5 µg/kg/day to about 2 mg/kg/day, to a subject. In additional embodiments, an antigen binding protein is administered to adults one time per week, two times per week, or three or more times per week, to treat an IGF-1 and/or IGF-2 mediated disease, condition or disorder, *e.g.*, a medical disorder disclosed herein. If injected, the effective amount of antigen binding protein per adult dose may range from 1-20 mg/m<sup>2</sup>, and preferably is about 5-12 mg/m<sup>2</sup>. Alternatively, a flat dose may be administered; the amount may range from 5-100 mg/dose. One range for a flat dose is about 20-30 mg per dose. In one embodiment of the invention, a flat dose of 25 mg/dose is repeatedly administered by injection. If a route of administration other than injection is used, the dose is appropriately adjusted in accordance with standard medical practices. One example of a therapeutic regimen involves injecting a dose of about 20-30 mg of antigen binding protein to one to three times per week over a period of at least three weeks, though treatment for longer periods may be necessary to induce the desired degree of improvement. For pediatric subjects (age 4-17), one exemplary suitable regimen involves the subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of antigen binding protein administered two or three times per week.

Particular embodiments of the methods provided herein involve subcutaneous injection of from 0.5 mg to 10 mg, preferably from 3 to 5 mg, of an antigen binding protein, once or twice per week. Another embodiment is directed to pulmonary administration (*e.g.*, by nebulizer) of 3 or more mg of antigen binding protein once a week.

Examples of therapeutic regimens provided herein comprise subcutaneous injection of an antigen binding protein once a week, at a dose of 1.5 to 3 mg, to treat a condition in which IGF-1R signaling plays a role. Examples of such conditions are provided herein and include, for example, cancer, acromegaly and other overgrowth disorders, diabetes, obesity, macular degeneration, and aging. Weekly administration of antigen binding protein is continued until a desired result is achieved, *e.g.*, the subject's symptoms subside. Treatment may resume as needed, or, alternatively, maintenance doses may be administered.

Other examples of therapeutic regimens provided herein comprise subcutaneous or intravenous administration of a dose of 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 15, or 20 milligrams of an IGF-1R inhibitor of the present invention per kilogram body mass of the subject (mg/kg). The dose can be administered once to the subject, or more than once at a certain interval, for example, once a day, three times a week, twice a week, once a week, three times a month, twice a month, once a month, once every two months, once every three months, once every six months, or once a year. The duration of the treatment, and any changes to the dose and/or frequency of treatment, can be altered or varied during the course of treatment in order to meet the particular needs of the subject.

In another embodiment, an antigen binding protein is administered to the subject in an amount and for a time sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the subject's illness, disease or condition may be assessed for determining whether the amount and time of the treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease

severity, symptoms, or manifestations of the disorder in question. In one embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four weeks. The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, biopsies, or other test results, and who may also employ  
5 questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease.

Elevated levels of IGF-1 and/or IGF-2 are associated with a number of disorders, including, for example, cancer (*e.g.*, lung, prostate, breast and colon cancers), and acromegaly and other overgrowth disorders (*e.g.*, constitutionally tall children). Subjects with a given disorder may be screened, to identify  
10 those individuals who have elevated IGF-1 and/or IGF-2 levels, thereby identifying the subjects who may benefit most from treatment with an IGF-1R binding antigen binding protein. Thus, treatment methods provided herein optionally comprise a first step of measuring a subject's IGF-1 and/or IGF-2 levels. An antigen binding protein may be administered to a subject in whom IGF-1 and/or IGF-2 levels are elevated above normal. In one embodiment, the present invention provides a method of treating an overgrowth  
15 disorder (*e.g.*, acromegaly) comprising administering to a subject in need thereof an antigen binding protein of the present invention and pegvisomant.

A subject's levels of IGF-1 and/or IGF-2 may be monitored before, during and/or after treatment with an antigen binding protein, to detect changes, if any, in their levels. For some disorders, the incidence of elevated IGF-1 and/or IGF-2 levels may vary according to such factors as the stage of the disease or the  
20 particular form of the disease. Known techniques may be employed for measuring IGF-1 and/or IGF-2 levels, *e.g.*, in a subject's serum. IGF-1 and/or IGF-2 levels in blood samples may be measured using any suitable technique, for example, ELISA.

Particular embodiments of methods and compositions of the invention involve the use of an antigen binding protein and one or more additional IGF-1R antagonists, for example, two or more antigen  
25 binding proteins of the invention, or an antigen binding protein of the invention and one or more other IGF-1R antagonists. In further embodiments, antigen binding protein are administered alone or in combination with other agents useful for treating the condition with which the patient is afflicted. Examples of such agents include both proteinaceous and non-proteinaceous drugs. When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art. "Co-  
30 administration" and combination therapy are not limited to simultaneous administration, but also include treatment regimens in which an antigen binding protein is administered at least once during a course of treatment that involves administering at least one other therapeutic agent to the patient.

Examples of other agents that may be co-administered with an antigen binding protein are other antigen binding proteins or therapeutic polypeptides that are chosen according to the particular condition to  
35 be treated. Alternatively, non-proteinaceous drugs that are useful in treating one of the particular conditions discussed above may be co-administered with an IGF-1R antagonist.

#### Combination therapy

In another aspect, the present invention provides a method of treating a subject with an IGF-1R  
40 inhibiting antigen binding protein and one or more other treatments. In one embodiment, such a

combination therapy achieves synergy or an additive effect by, for example, attacking multiple sites or molecular targets in a tumor. Types of combination therapies that can be used in connection with the present invention include inhibiting or activating (as appropriate) multiple nodes in a single disease-related pathway, multiple pathways in a target cell, and multiple cell types within a target tissue (e.g., within a tumor). For example, an IGF-1R inhibitor of the present invention can be combined with a treatment that inhibits IGF-1, promotes apoptosis, inhibits angiogenesis, or inhibits macrophage. In another embodiment, a targeted agent, that, when used by itself, fails to elicit a therapeutically desired effect, could be used to, for example, sensitize cancer cells or augment treatment effect of other agents. In another embodiment, an IGF-1R inhibitor according to the invention is used in combination with a cytotoxic drug or other targeted agent that induces apoptosis. In another embodiment, an IGF-1R inhibitor is used in combination with one or more agents that inhibit different targets that are involved in cell survival (e.g., PKB, mTOR), different receptor tyrosine kinases (e.g., ErbB1, ErbB2, c-Met, c-kit), or different cell types (e.g., KDR inhibitors, c-fms). In another embodiment, an IGF-1R inhibitor of the invention is added to the existing standard of care for a particular condition. Examples of therapeutic agents include, but are not limited to, gemcitabine, taxol, taxotere, and CPT-11.

In another embodiment, a combination therapy method comprises administering to the subject two, three, four, five, six, or more of the IGF-1R agonists or antagonists described herein. In another embodiment, the method comprises administering to the subject two or more treatments that together inhibit or activate (directly or indirectly) IGF-1R-mediated signal transduction. Examples of such methods include using combinations of two or more IGF-1R inhibiting antigen binding proteins, of an IGF-1R inhibiting antigen binding protein and one or more other IGF-1, IGF-2, and/or IGF-1R agonists or antagonists (e.g., IGF-1 and/or IGF-2 binding polypeptides, IGF-1R binding polypeptides, IGF-1 and/or IGF-2 derivatives, anti-IGF-1 and/or IGF-2 antibodies, anti-sense nucleic acids against IGF-1, IGF-2, and/or IGF-1R, or other molecules that bind to IGF-1, IGF-2, and/or IGF-1R polypeptides or nucleic acids), or of an IGF-1R inhibiting antigen binding protein and one or more other treatments (e.g., surgery, ultrasound, radiotherapy, chemotherapy, or treatment with another anti-cancer agent), as described, for example, in US Pat. No. 5,473,054 (issued Dec. 5, 1995), 6,051,593 (issued April 18, 2000), 6,084,085 (issued July 4, 2000), 6,506,763 (issued Jan. 14, 2003), US Pat. App. Pub. No.s 03/0092631 (published May 15, 2003), 03/0165502 (published Sept. 4, 2003), 03/0235582 (published Dec. 25, 2003), 04/0886503 (published May 6, 2004), 05/0272637 (published Dec. 8, 2005), PCT Pub. Ser. No.s WO 99/60023 (published Nov. 25, 1999), WO 02/053596 (published July 11, 2002), WO 02/072780 (published Sept. 19, 2002), WO 03/027246 (published March 3, 2003), WO 03/020698 (published March 13, 2003), WO 03/059951 (published July 24, 2003), WO 03/100008 (published Dec. 4, 2003), WO 03/106621 (published Dec. 24, 2003), WO 04/071529 (published August 26, 2004), WO 04/083248 (published Sept. 30, 2004), WO 04/087756 (published Oct. 14, 2004), WO 05/112969 (published Dec. 1, 2005), Kull *et al.*, 1983, J Biol Chem 258:6561-66, Flier *et al.*, 1986, Proc Natl Acad Sci USA 83:664-668, Conover *et al.*, 1987, J Cell Physiol 133:560-66, Rohlik *et al.*, 1987, Biochem Biophys Res Comm 149:276-81, Arteaga *et al.*, 1989, J Clinical Investigation 84:1418-23, Arteaga *et al.*, 1989, Cancer Res 49:6237-41, Gansler *et al.*, 1989, American J Pathol 135:961-66, Gustafson *et al.*, 1990, J Biol Chem 265:18663-67, Steele-Perkins *et al.*, 1990, Biochem Biophys Res Comm 171:1244-51, Cullen *et al.*, 1992, Mol Endocrinol 6:91-100, Soos *et*

5 *al.*, 1992, J Biol Chem 267:12955-63, Xiong *et al.*, 1992, Proc Natl Acad Sci USA 89:5356-60, Brunner *et al.*, 1993, Euro J Cancer 29A:562-69, Furlanetto *et al.*, 1993, Cancer Res 53:2522-26, Li *et al.*, 1993, Biochem Biophys Res Comm 196:92-98, Kalebic *et al.*, 1994, Cancer Res 54:5531-34, Lahm *et al.*, 1994, Intl J Cancer 58:452-59, Zia *et al.*, 1996, J Cell Biochem Supp 24:269-75, Jansson *et al.*, 1997, J Biol Chem  
 10 272:8189-97, Scotlandi *et al.*, 1998, Cancer Res 58:4127-31, Logie *et al.*, 1999, Li *et al.*, 2000, Cancer Immunol Immunotherapy 49:243-52, J Mol Endocrinol 23:23-32, De Meyts *et al.*, 2002, Nature Reviews 1:769-83, Hailey *et al.*, 2002, Mol Cancer Therapeutics 1:1349-53, Maloney *et al.*, 2003, Cancer Research 63:5073-83, Burtrum *et al.*, 2003, Cancer Research 63:8912-21, and Karavitaki *et al.*, 2004, Hormones 3:27-36, (each incorporated herein by reference in its entirety) may be employed in methods and  
 15 compositions of the present invention. Furthermore, one or more anti-IGF-1R antibodies or antibody derivatives can be used in combination with one or more molecules or other treatments, wherein the other molecule(s) and/or treatment(s) do not directly bind to or affect IGF-1R, IGF-1, or IGF-2, but which combination is effective for treating or preventing a condition, such as cancer or an overgrowth disorder (*e.g.*, acromegaly). In one embodiment, one or more of the molecule(s) and/or treatment(s) treats or  
 20 prevents a condition that is caused by one or more of the other molecule(s) or treatment(s) in the course of therapy, *e.g.*, nausea, fatigue, alopecia, cachexia, insomnia, *etc.* In every case where a combination of molecules and/or other treatments is used, the individual molecule(s) and/or treatment(s) can be administered in any order, over any length of time, which is effective, *e.g.*, simultaneously, consecutively, or alternately. In one embodiment, the method of treatment comprises completing a first course of  
 25 treatment with one molecule or other treatment before beginning a second course of treatment. The length of time between the end of the first course of treatment and beginning of the second course of treatment can be any length of time that allows the total course of therapy to be effective, *e.g.*, seconds, minutes, hours, days, weeks, months, or even years.

30 In another embodiment, the method comprises administering one or more of the IGF-1R antagonists described herein and one or more other treatments (*e.g.*, a therapeutic or palliative treatment), for example, anti-cancer treatments (such as surgery, ultrasound, radiotherapy, chemotherapy, or treatment with another anti-cancer agent). Where a method comprises administering more than one treatment to a subject, it is to be understood that the order, timing, number, concentration, and volume of the  
 35 administrations is limited only by the medical requirements and limitations of the treatment, *i.e.*, two treatments can be administered to the subject, *e.g.*, simultaneously, consecutively, alternately, or according to any other regimen. Examples of agents that can be administered in combination with the IGF-1R antagonists described herein include, but are not limited to, neutrophil-boosting agents, irinotecan, SN-38, gemcitabine, herstatin, or an IGF-1R-binding herstatin derivative (as described, for example, in US Pat.  
 40 App. No. 05/0272637), AVASTIN® (Genentech, South San Francisco, CA), HERCEPTIN® (Genentech), RITUXAN® (Genentech), ARIMIDEX® (AstraZeneca, Wilmington, DE), IRESSA® (AstraZeneca), BEXXAR® (Corixa, Seattle, WA), ZEVALIN® (Biogen Idec, Cambridge, MA), ERBITUX® (Imclone Systems Inc., New York, NY), GEMZAR® (Eli Lilly and Co., Indianapolis, IN), CAMPTOSAR® (Pfizer, New York, NY), GLEEVEC® (Novartis), SU-11248 (Pfizer), BMS-354825 (Bristol-Myers Squibb), panitumumab (Abgenix, Fremont, CA/Amgen Inc., Thousand Oaks, CA), and denosumab (Amgen Inc.,  
 45 Thousand Oaks, CA).

The following examples, both actual and prophetic, are provided for the purpose of illustrating specific embodiments or features of the instant invention and do not limit its scope.

#### EXAMPLE 1: Preparation of Antibodies

5           This example demonstrates a method of preparing antibodies recognizing the IGF-1 receptor. IGF-1 receptor polypeptides may be employed as immunogens in generating monoclonal antibodies by conventional techniques. It is recognized that polypeptides in various forms may be employed as immunogens, *e.g.*, full length proteins, fragments thereof, fusion proteins thereof such as Fc fusions, cells expressing the recombinant protein on the cell surface, *etc.*

10           To summarize an example of such a procedure, an IGF-1R immunogen emulsified in complete Freund's adjuvant is injected subcutaneously into Lewis rats, in amounts ranging from 10-100  $\mu$ l. Three weeks later, the immunized animals are boosted with additional immunogen emulsified in incomplete Freund's adjuvant and boosted every three weeks thereafter. Serum samples are periodically taken by retro-orbital bleeding or tail-tip excision for testing by dot-blot assay, ELISA (enzyme-linked immunosorbent  
15           assay), or inhibition of binding of  $^{125}$ I-IGF-1 or  $^{125}$ I-IGF-2 to extracts of IGF-1R-expressing cells. Following detection of an appropriate antibody titer, positive animals are given a final intravenous injection of antigen in saline. Three to four days later, the animals are sacrificed, splenocytes harvested, and fused to the murine myeloma cell line AG8653. The resulting hybridoma cell lines are plated in multiple microtiter plates in a HAT selective medium (hypoxanthine, aminopterin, and thymidine) to inhibit proliferation of  
20           non-fused cells, myeloma hybrids, and spleen cell hybrids.

          Hybridoma clones thus generated are screened for reactivity with IGF-1R. Initial screening of hybridoma supernatants utilizes an antibody capture and binding of partially purified  $^{125}$ I-IGF-1 receptor. Hybridomas that are positive in this screening method are tested by a modified antibody capture to detect hybridoma cells lines that are producing blocking antibody. Hybridomas that secrete a monoclonal  
25           antibody capable of inhibiting  $^{125}$ I-IGF-1 binding to cells expressing IGF-1R are thus detected. Such hybridomas then are injected into the peritoneal cavities of nude mice to produce ascites containing high concentrations (>1 mg/ml) of anti-IGF-1R monoclonal antibody. The resulting monoclonal antibodies may be purified by ammonium sulfate precipitation followed by gel exclusion chromatography, and/or affinity chromatography based on binding of antibody to Protein G.

30           Similar methods can be used to generate human antibodies in transgenic mice. See, *e.g.*, Chen *et al.*, 1993, *Internat. Immunol.* 5: 647-56; Chen *et al.*, 1993, *EMBO J.* 12: 821-30; Choi *et al.*, 1993, *Nature Genetics* 4: 117-23; Fishwild *et al.*, 1996, *Nature Biotech.* 14: 845-51; Harding *et al.*, 1995, *Annals New York Acad. Sci.*; Lonberg *et al.*, 1994, *Nature* 368: 856-59; Lonberg, 1994, *Handbook Exper. Pharmacol.* 113: 49-101; Lonberg *et al.*, 1995, *Internat. Rev. Immunol.* 13: 65-93; Morrison, 1994, *Nature* 368: 812-13;  
35           Neuberger, 1996, *Nature Biotech.* 14: 826; Taylor *et al.*, 1992, *Nuc. Acids Res.* 20: 6287-95; Taylor *et al.*, 1994, *Internat. Immunol.* 6: 579-91; Tomizuka *et al.*, 1997, *Nature Genetics* 16: 133-43; Tomizuka *et al.*, 2000, *Proc. Nat. Acad. Sci. USA* 97: 722-27; Tuailon *et al.*, 1993, *Proc. Nat. Acad. Sci. USA* 90: 3720-24; Tuailon *et al.*, 1994, *J. Immunol.* 152: 2912-20; Russel *et al.*, 2000, *Infection and Immunity* April 2000: 1820-26; Gallo *et al.*, 2000, *Eur. J. Immunol.* 30: 534-40; Davis *et al.*, 1999, *Cancer Metastasis Rev.*  
40           18:421-25; Green, 1999, *J. Immunol. Methods* 231:11-23; Jakobovits, 1998, *Advanced Drug Delivery Rev.*

- 31:33-42; Green *et al.*, 1998, J. Exp. Med. 188: 483-95; Jakobovits, 1998, Exp. Opin. Invest. Drugs 7: 607-14; Tsuda *et al.*, 1997, Genomics 42: 413-21; Mendez *et al.*, 1997, Nature Genetics 15: 146-56; Jakobovits, 1996, Weir's Handbook of Experimental Immunology, The Integrated Immune System Vol. IV, 194.1-194.7; Mendez *et al.*, 1995, Genomics 26: 294-307; Jakobovits, 1994, Current Biol. 4: 761-63; Arbones, 1994, Immunity 1: 247-60; Green *et al.*, 1994, Nature Genetics 7: 13-21; Jakobovits *et al.*, 1993, Nature 362: 255-58; Jakobovits *et al.*, 1993, Proc. Nat. Acad. Sci. USA 90: 2551-55.

#### EXAMPLE 2: Isolation of Human IGF-1R(ECD)-C3-muIgG1

This example provides a method of making a soluble fragment of IGF-1R useful for raising antibodies.

##### Cloning of pDSR $\alpha$ :huIGF-1R(ECD)-C3-muIgG1Fc

Primers 2830-36:

- 5' AGCAAGCTTCCACCATGAAGTCTGGCTCCGGAGGAGG 3' SEQ ID NO:256)  
and 2830-38:  
5' ATTTGTCGACTTCGTCCAGATGGATGAAGTTTTCAT 3', SEQ ID NO:257)
- were used to amplify the human IGF-1R extracellular domain (1-906) cDNA sequence. The primers included a Kozak translation initiation sequence (underlined above) preceding the start codon, restriction sites for subsequent subcloning, and a caspase-3 site, which is inserted next to the extracellular domain C-terminus. PCR was performed on a PerkinElmer 2400 (PerkinElmer, Torrance, CA) under the following conditions: 1 cycle at 95° C for 2 min, 23 cycles at 95° C for 30 sec, 58.5° C for 30 sec, and 72° C for 3 min, and 1 cycle at 72° C for 10 min. Final reaction conditions were 1X *pfu* TURBO® buffer (Stratagene, La Jolla, CA), 200  $\mu$ M dNTPs, 2  $\mu$ M each primer, 5 U *pfu* TURBO® (Stratagene) and 1 ng template DNA. The PCR product was purified using a Clontech Nucleospin Column (Clontech, Palo Alto, CA) according to the manufacturers instructions, digested with *Hind* III and *Sal* I (Roche, Indianapolis, IN) and gel purified. The human IGF-1R insert was ligated into *Hind* III/*Sal* I digested pDSR $\alpha$ -muIgG1. Integrity of the insert was confirmed by DNA sequencing. The sequence of the protein encoded by the resulting open reading frame (IGF-1R-C3-muFc) is shown in Figure 10. The final expression vector, pDSR $\alpha$ :huIGF1R(ECD)-C3-muIgG1Fc, is described in Table 1.

Table 1

##### pDSR $\alpha$ :huIGF1R(ECD)-C3-muIgG1Fc

Plasmid Base

Pair Number:

11-3496	HuIGF1R (Caspase 3 site)-muIgG1Fc atgaagctcggctccggaggagggtcccgacctcgtgtgggggctcctgtttctcctccgcccgcgtctcgtctcgtccga cgagtgagaaatctgcgggcccaggcatcgacatccgcaacgactatcagcagctgaagcgcctggagaactgcacggt gatcgagggtacccacatcctgctcatctccaaggccgaggactaccgcagctaccgcttcccaagctacgggtcatt accgagtactgtgtgttcagggtggctggcctcgagagcctcgagacaccttccccaaacctcacgggtatccgcggt ggaaactcttacaactacgcctgtcatcttcgagatgaccaatctcaaggatattgggtttacaacctgaggaacattac tcggggggccatcaggattgagaaaaatgtgacctctgttacctctccactgtggactggctcctgatcctggatgcggtgt ccaataactacattgtggggaataagccccaaaggatgtggggacctgtgtccagggaacctgaggagaaagccgatg tgtgagaagaccaccatcaacaatgagtacaactaccgctgtggaccacaaaccgctgccagaaaatgtgccaagcac gtgtgggaagcggcggtgcaccgagaacaatgagtgtgtccaccccgagtgccctgggcagctgcagcgcgcctgacaa
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	cgacacggcctgtgtagcttgcggccactactactatgccgggtgtgtgtgctgctgcccggcccaacacctacaggtttg agggtgtggcgtgtgtggaccgtgacttctgcgccaacatcctcagcgccgagagcagcactccgaggggtttgtgatcc acgacggcgagtgcatgcaggagtgcccctcgggtcttccgcaacggcgagccagagcatgtactgcatccctgttgaa ggctccttggccgaagggtgtgtgaggaagaaagaaacaagaccattgattctgttacttctgctcagatgtccaaagatg caccatctcaagggaatttgcctcattaacatccgacgggggaataacattgcttcagagctggagaacttcatggggctcal cgaggtgtgtgacgggtacgtgaagatccgcaattctcatgcttgggtctccttgccttcciaaaaaaccttgcctcatccta ggagaggagcagctagaagggaattactccttctacgtctcgcacaaccagaactgacgaactgtgggactgggaccac cgcaacctgacctcaaagcagggaattgtacttgccttcaatcccaattatgtgttccgaaatttaccgcatggaggaa gtgacggggactaaaggcgccaaagcaaggggacataaacaccagggaacaacaggagagcctcctgtgaaagt gacgtcctgcattcactccaccaccacgtcgaagaatgcacatcataacctggcaccgggtaccggccccctgactaca gggatctcatcagcttaccgtttactacaagggaagcaccctttaagaatgtcacagagtatgatgggcaggatgcctgcggc tccaacagctggaacatggtggacgtggacctcccgcccaacaaggacgtggagcccgcatcttactacatgggtgaa gccttgactcagtagccgtttacgtcaaggctgtgacctcaccatggtggagaacgacctatccgtggggccaagag tgagatctgtacattgcaccaatgctcagttccttccattcccttggacgttcttccagcatcgaactcctctctcagtaatcg tgaagtggaaacctcctctctgtcccaacggcaacctgagtactacattgtgcgctggcagcggcagcctcaggacggcta cctttaccggcacaattactgctccaaagacaaaatcccatcagggaagtatgcgacggcaccatcgacattgaggaggtc acagagaaccccaagactgaggtgtgtgtggggagaaaggccttgcctgccttgccttcccaaaactgaagccgagaagc aggccgagaaggaggaggtgtaataccgcaagcttcttgagaattcctgcacaactccatctcgtgccagacctgaaag gaagcggagagatgtcatgcaagtggccaacaccacattgtccagccgaagcagggaacaccacggcccgaggaacaccta caacatcactgacctgggaagagctggagacagagtacccttcttggagagcagagtggataacaaggagagaactgtcatt tctaaccttgcgctttcattgtaccgcatcgatatccacagctgcaaccacgaggctlgagaagctgggctgcagcgctc caacttgccttgcgaaggactatgcccgagaaggagcagatgacattcctggccagtgacctgggagccaaggcctga aaactccatcttttaagtgccggaacctgagaatcccaatggattgattctaattgatgaataaaatcggatcacaagtt gaggatcagcgagaatgtgtgtccagacaggaatacaggaagtatggaggggccaagctaaaccgggtaaaaccgggga actacacagcccgattcagggccacatctctcttgggaatgggtcgtggacagatcctgtgttcttctatgtccagccaaaa caggatatgaaaacttcatcctctgacgaagtcgacgggtgtaagccttgcataatgtacagtcccagaagtatcctgtctt catcttcccccaaggccaagatgtgtcaccattactctgactcctaaggtcacgtgtgtgtgtgtagacatcagcaagga tgatcccgaggtccagttcagctggttctgatgatgtggagggtgcacacagctcagacgcaacccgggagggagcagtt caacagcacttccgctcagtcagtgaaacttccatcctgaccaggactggctcaatggcaaggagttcaaatgcagggtgta aacagtgacgttccctgcccccatcgagaaaacacatctccaaaaccaaaggcagaccgaaggctccacaggtgtacacc attccacitcccaaggagcagatggccaaggataaagtcagctgtgacctgcatgataacagacttcttccctgaagacattac tgtggagtggcagtggaatgggcagccagcgagaaactacaagaacactagcccatctggacacagatggctcttactt cgtctacagcaagctcaatgtgcagaagagcaactgggaggcaggaatacttccctgctctgtgtataggggcctg cacaaccaccatactgagaagaccccttccactctcctgtgtaa (SEQ ID NO:258)
3507 to 4391	A transcription termination/polyadenylation signal from the $\alpha$ -subunit of the bovine pituitary glycoprotein hormone ( $\alpha$ -FSH) (Goodwin <i>et al.</i> , 1983, <i>Nucleic Acids Res.</i> 11:6873-82; Genbank Accession Number X00004)
4600 to 5163	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser <i>et al.</i> , 1982, <i>Proc. Natl. Acad. Sci. U. S. A.</i> 79:6522-6; Nunberg <i>et al.</i> , 1980, <i>Cell</i> 19:355-64; Setzer <i>et al.</i> , 1982, <i>J. Biol. Chem.</i> 257:5143-7; McGrogan <i>et al.</i> , 1985, <i>J. Biol. Chem.</i> 260:2307-14)
6389 to 7246	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in <i>E. coli</i> (Genbank Accession Number J01749)
7459 to 7802	An SV40 early promoter, enhancer and origin of replication (Takebe <i>et al.</i> , 1988, <i>Mol. Cell Biol.</i> 8:466-72, Genbank Accession Number J02400)
7809 to 8065	A translational enhancer element from the HTLV-1 LTR domain (Seiki <i>et al.</i> , 1983, <i>Proc. Natl. Acad. Sci. U. S. A.</i> 80:3618-22, Genbank Accession Number J02029)
8109 to 8205	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983, <i>Mol. Cell Biol.</i> 3:280-9, Genbank Accession Number J02400)

#### Expression of hu IGF-1R(ECD)-C3-muIgG1Fc

Fifteen micrograms of linearized expression vector pDSR $\alpha$ :huIGF1R(ECD)-C3-muIgG1Fc was transfected into AM-1/D CHO $\alpha$ - cells using LT1 lipofection reagent (PanVera Corp., Madison, WI), and cells cultured under conditions to allow expression and secretion of protein into the cell media. Twenty-four colonies were selected after 10-14 days on DHFR selection medium (Dulbecco's Modified Eagles

Medium (Invitrogen) supplemented with 10% dialyzed fetal bovine serum, 1x penicillin-streptomycin (Invitrogen)) and expression levels evaluated by western blot. To perform this assay, 0.5 ml of serum free medium was added to a single well confluent cells cultured in a 24 well plate (Falcon). The conditioned medium was recovered after 48hr. Samples for western blotting were run in 10% Tris-glycine gel (Novex), and blotted on 0.45  $\mu$ m Nitrocellulose membrane (Invitrogen), using the Mini Trans-Blot cell (Biorad). The blotted membranes were incubated with rabbit anti-mouse IgG Fc antibody, conjugated with Horseradish Peroxidase (Pierce). The clone expressing the highest level of IGF-1R(ECD)-C3-muIgG1Fc was expanded in DHFR selection medium and  $2 \times 10^7$  cells were inoculated into 50 roller bottles each (Corning) in 250 ml of high-glucose DMEM (Invitrogen), 10% dialyzed FBS (Invitrogen), 1x glutamine (Invitrogen), 1x Non essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen). Medium was gassed with 10% CO<sub>2</sub>/balance air for 5 seconds before capping the roller bottle. Roller bottles were kept at 37° C on roller racks spinning at 0.75 rpm.

When cells reached approximately 85-90% confluency (after approximately 5-6 days in culture), growth medium was discarded, cells washed with 100 ml PBS and 200 ml production medium was added (50 % DMEM (Invitrogen)/ 50 % F12 (Invitrogen), 1x glutamine (Invitrogen), 1x non-essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen), 1.5% DMSO (Sigma)). The conditioned medium was harvested and replaced at one week intervals. The resulting 30 liters of conditioned medium were filtered through a 0.45  $\mu$ m cellulose acetate filter (Corning, Acton, MA).

#### Purification of hu IGF-1R(ECD)-C3-muIgG1Fc

The resulting filtrate from the conditioned medium was concentrated 20-fold using a spiral-wound cartridge (molecular weight cut-off = 10 kDa), then diluted 1:1 with 3 M KCl, 1 M glycine, pH 9.0 to bring the final salt concentration to 1.5 M KCl, 0.5 M glycine, pH 9.0. This sample was applied to a rProtein A-Sepharose column (Amersham Pharmacia Biotech, Uppsala, Sweden) which had been equilibrated in 1.5 M KCl, 0.5 M glycine, pH 9.0. The column was washed with 40 column volumes of the same buffer, then eluted with 20 column volumes of 0.1 M glycine-HCl, pH 2.8. Five-mL fractions were collected and immediately neutralized with 1 mL of 1 M Tris-HCl, pH 7.5. Fractions containing huIGF1R(ECD)-C3-muIgGFc were identified by SDS-PAGE, pooled, and dialyzed against phosphate-buffered saline. The yield was 2.4 mg/L of conditioned medium. The major protein species detected were the mature  $\alpha$  and  $\beta$  chains and murine Fc, each of which appeared to be properly glycosylated based on their elevated and heterogeneous molecular weights. Unprocessed IGF-1R(ECD), as well as glycosylated but not proteolytically cleaved IGF-1R(CED), was also present in the preparation. The shift in bands to higher molecular weights under non-reducing conditions indicates that disulfide linkages joined the  $\alpha$  and  $\beta$  chains. Amino-terminal sequencing of the final product indicated that 60% of the protein was correctly processed between the  $\alpha$ - and  $\beta$ -chains of IGF-1R(ECD), while 40% remained unprocessed.

#### EXAMPLE 3: Isolation of Human INSR(ECD)-muIgG1

This example presents a method of cloning and expressing a soluble fragment of the human insulin receptor.

#### Cloning of pDSR $\alpha$ :huINSR(ECD)-muIgG1Fc





	gggaaatgtgacgggtggccgtgcccacgggtggcagcttccccaacacttctcgaccagcgtgcccacgagtcggagga gcacaggccttttgagaaggtgtgaacaaggagtcgctggtcatctccggcttgcgacacttcacgggctatcgcatcgag ctgcaggcttgcaaccaggacacccctgaggaacgggtcagtggtgagcctacgtcagtgcgaggaccatgcctgaagc caaggctgatgacattgttgccctgtgacgcatgaaatctttgagaacaacgtcgtccacttgatgtggcaggagccgaag gagcccaatggctgacgtgtgtgtatgaagtgaattatcgccgatatggtgatgaggagctgcactctcgtctcccgaa gcacttcgctctggaacggggctgcaggctgcgtgggctgtcaccggggaactacagcgtgcgaatccgggccacctccc ttgcgggcaacggctcttgacggaaccacacatttctacgtgacagactatttagcgtcccgtaaatattgcaaaagtcg acggtgtgaagccttgcatatgtacagtcaccagaagtatcatctgtcttcatcttcccccaagcccaaggatgtgtcaccat tactctgactcctaaggtcacgtgtgtgtgtagacatcagcaaggatgatcccagggtccagttcagctgtgtgtgatgat gtggagggtgcacacagctcagacgcaacccgggaggagcagttcaacagcacttccgctcagtcagtgaaattcccatc atgcaccaggactggctcaatggcaaggagtcaaatgcagggttaacagtgacgtttccctgcccccatcgagaaaacc atctccaaaacaaaggcagaccgaaggctccacaggtgtacaccattccacctccaaggagcagatggccaaggataa agtcagcttgacctgcatgataacagacttctccctgaagacattactgtggagtggcagtggaatgggcagccagcgag aactacaagaacactcagcccatcatggacacagatggcttacttctgtacagcaagctcaatgtgcagaagagcaact gggaggcaggaatactttcacctgctgtgtgtatgatgaggcctgcacaaccaccatactgagaagacgtctctccactct cctggtaaa (SEQ ID NO:261)
3557 to 4441	A transcription termination/polyadenylation signal from the $\alpha$ -subunit of the bovine pituitary glycoprotein hormone ( $\alpha$ -FSH) (Goodwin <i>et al.</i> , 1983, <i>Nucleic Acids Res.</i> <b>11</b> :6873-82; Genbank Accession Number X00004)
4446 to 5586	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser <i>et al.</i> , 1982, <i>Proc. Natl. Acad. Sci. U. S. A.</i> <b>79</b> :6522-6; Nunberg <i>et al.</i> , 1980, <i>Cell</i> <b>19</b> :355-64; Setzer <i>et al.</i> , 1982, <i>J. Biol. Chem.</i> <b>257</b> :5143-7; McGrogan <i>et al.</i> , 1985, <i>J. Biol. Chem.</i> <b>260</b> :2307-14)
5594 to 6241	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in <i>E. coli</i> (Genbank Accession Number J01749)
7513 to 7856	An SV40 early promoter, enhancer and origin of replication (Takebe <i>et al.</i> , 1988, <i>Mol. Cell Biol.</i> <b>8</b> :466-72, Genbank Accession Number J02400)
7863 to 8119	A translational enhancer element from the HTLV-1 LTR domain (Seiki <i>et al.</i> , 1983, <i>Proc. Natl. Acad. Sci. U. S. A.</i> <b>80</b> :3618-22, Genbank Accession Number J02029)
8163 to 8259	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983, <i>Mol. Cell Biol.</i> <b>3</b> :280-9, Genbank Accession Number J02400)

#### Expression of hu INSR(ECD)-C3-muIgG1Fc

AM-1/D CHO<sup>d</sup>- cells were transfected with 15  $\mu$ m of linearized expression vector pDSRa:huINSR(ECD) –muIgG1Fc using FUGENE™ 6 lipofection reagent (Roche Diagnostics Corp., Indianapolis, IN), then cultured under conditions to allow expression and secretion of protein into the cell medium. Colonies were selected and analyzed as described above.

#### Purification of hu INSR(ECD)-C3-muIgG1Fc

The filtered conditioned medium containing huINSR(ECD)-muIgGFc was concentrated 17-fold using a spiral-wound cartridge (molecular weight cut-off = 10 kDa), then diluted 1:1 with 3 M KCl, 1 M glycine, pH 9.0 to bring the final salt concentration to 1.5 M KCl, 0.5 M glycine, pH 9.0. This sample was applied to a rProtein A-Sepharose column (Pharmacia) which had been equilibrated in 1.5 M KCl, 0.5 M glycine, pH 9.0. The column was washed with 40 column volumes of the same buffer, then eluted with 20 column volumes of 0.1 M glycine-HCl, pH 2.8. Five-mL fractions were collected and immediately neutralized with 1-mL of 1 M Tris-HCl, pH 7.5. Fractions containing huINSR(ECD)-muIgGFc were identified by SDS-PAGE, pooled, and dialyzed against phosphate-buffered saline. The yield was 0.9 mg/L of conditioned medium. The major protein species were the mature  $\alpha$  and  $\beta$  chains and murine Fc. Each of these species appeared to be properly glycosylated based on its elevated and heterogeneous molecular

weight. Unprocessed INSR (ECD) as well as glycosylated but not proteolytically cleaved INSR (CED) also was present in the preparation. The shift in bands to higher molecular weights under non-reducing conditions indicated that disulfide linkages joined the  $\alpha$  and  $\beta$  chains. Amino-terminal sequencing of the final product indicated that 87% of the protein was correctly processed between the  $\alpha$ - and  $\beta$ -chains of INSR(ECD), while 13% remained unprocessed.

### EXAMPLE 3: Initial Screen for Anti-IGF-1R phage Fab

This example provides a method of identifying anti-IGF-1R antibodies.

A Target Quest Q Fab library ("the TQ library"; Target Quest, Maastricht, the Netherlands), which was constructed using peripheral blood lymphocytes from four healthy donors and splenic lymphocytes from one patient with gastric carcinoma, was obtained. The library diversity was  $3.7 \times 10^{10}$  clones, containing  $3 \times 10^9$  heavy chains. The source, screening methods, and characterization of the library have been published (de Haard *et al*, 1999, J Biol Chem 274:18218-30). Dynabeads (200  $\mu$ l) M-450 Uncoated (catalog # 140.02, Dynal, Lake Success, NY) were washed 3 times with PBS, resuspended in 200  $\mu$ l of IGF1R(ECD)-C3-mFc to a concentration of 0.5  $\mu$ M in PBS, and incubated at 4° C on a rotator overnight. The IGF-1R(ECD)-C3-mFc coated beads were washed 3x with 1 ml of 2% non-fat dry milk (M) in PBS (2% MPBS), and then blocked with 1 ml of 2% MPBS at room temperature for 1 hour. In parallel, 750  $\mu$ l of the TQ library ( $4 \times 10^{12}$  pfu) was preblocked by mixing with 250  $\mu$ l 8% MPBS at room temperature for 30 minutes to 1 hour. 500  $\mu$ l of blocked beads were transferred into another microfuge tube and separated from the blocking solution on a magnetic separator. The preblocked phage mixture was added to the blocked beads and incubated for 90 minutes on a rotator at room temperature. Bead-bound phage were separated from the unbound phage, and then washed 6x with 1ml 2% MPBS/0.1% Tween 20, 6x with 1ml PBS/0.1% Tween 20, 2x with PBS with a change of tubes between different wash solutions. Bound phage was eluted with 1 ml of 0.1M TBA (pH11) for 10 minutes, then immediately separated from the beads and neutralized with 0.5 ml of 1 M Tris.HCl. The eluted phage pool was mixed with 4 ml 2x YT broth (10 g yeast extract, 16 g bacto-tryptone, 5 g NaCl per liter of water) and 5 ml of TG1 bacterial culture (O.D.<sub>590</sub> about 0.5) in a 50-ml conical tube. The infection mixture was incubate at 37° C in an incubator for 30 min., then centrifuged at 3500 rpm for 20 min. The cell pellet was resuspended in 1500  $\mu$ l 2xYT-CG broth and 300  $\mu$ l were spread on each of five 2xYT-CG (2x YT broth containing 100  $\mu$ g/ml carbenicillin and 2% glucose) plates. After 20 hours of incubation at 30° C, 4 ml of 2x YT-AG were added to each plate and the cells were recovered with cell scraper from the plates. This step was repeated three times. A small portion of the recovered cells was used for phage rescue (see below). The remaining cell suspension was centrifuged at 3500 rpm for 20 min. The cell pellet was suspended into an amount of 50% glycerol roughly half the volume of the pellet size and stored at -80° C.

In order to rescue phage, the plated-amplified cell suspension was used to inoculate 40 ml of 2x YT-CG to an OD<sub>590</sub> of about 0.05. The culture was incubated at 37° C on a shaker to OD<sub>590</sub> 0.5. The log phase culture was infected with M13KO7 helper phage (GIBCO BRL, Gaithersburg, MD, catalog # 18311-019,  $1.1 \times 10^{11}$  pfu/ml) at M.O.I. 20 followed by incubation at 37° C for 30 min. The infected cells were centrifuged at 4000 rpm for 20 min. The cell pellet was re-suspended in 200 ml of 2xYT-CK (100  $\mu$ g/ml

carbenicillin and 40 µg/ml kanamycin) and transferred to two 250-ml flasks and incubated at 30° C with shaking at 270 rpm for 20 hours. The over-night culture was centrifuged at 4000 rpm for 20 min to removal cell debris. The centrifugation was repeated to ensure the removal of cell debris. About 1/5 volume of PEG solution (20% PEG 8000, 2.5 M NaCl) was added to the supernatant to precipitate the phage particles. 5 The mixture was incubated on ice for at least 1 hour, followed by centrifugation at 4000 rpm for 20 min to collect the precipitated phage particles. The phage pellet was re-suspended into 1 ml of PBS and transferred to a microfuge tube. The phage suspension was left on ice for 1 hour to allow complete suspension of phage particles, and clarified by centrifugation at 14,000 rpm for 2 min to remove the residual cell debris. Phage precipitation step was repeated. The final phage pellet was suspended into PBS 10 after clarification. The rescued phage suspension was used in the next round of selection.

Four rounds of selection were performed that included alterations of various standard binding parameters. The second round of selection was identical to the first round of selection. Variations in input phage number and elution reagent were introduced in rounds three and four. For the round three selection, 5x10<sup>11</sup> pfu of phages were selected and bound phages were eluted either with 1 µM IGF-1 (catalog # I3769, 15 Sigma, St. Louis, MO) or with a 1 µM concentration of a chimeric αIR3-huFc antibody to yield two round-three pools, TQ4-3IS and TQ4-3CA. Round four selection was carried out on rescued phage pools from both round three pools. Two rounds of negative selection with mouse IgG Fc-coated DYNABEADS® (Dynal Biotech, Oslo, Norway) were included to remove mouse Fc binders prior to actual IGF-1R selection. The incubation time for negative selection was 30 minutes each. 3.78x10<sup>11</sup> pfu of TQ4-3IS pool and 20 3.75x10<sup>12</sup> pfu of TQ4-3CA pool were selected separately. Bound phage were eluted with 1 µM IGF-2 (catalog # I2526, Sigma, St. Louis, MO) to yield two round-4 pools, TQ4-4ISI2 and TQ4-4CAI2. The sequence of about 96-192 phage DNA inserts was determined at each elution step.

In some cases, a secondary screen was done. Phagemid DNA mixtures of the total TQ library, and the selected phage amplified after several rounds of selection against IGF-1R, were prepared using a DNA 25 Maxiprep kit according to the manufacturer's instructions (Qiagen, Valencia, CA). All four DNA preparations were digested with *Asc* I and *Eco*R I (New England Biolab, Beverly, MA). The resulting two *Asc* I/*Eco*R I fragments were separated on preparative 0.5% agarose gels. The 2.1 kb fragments containing heavy chains were gel purified from the IGF-1R selected phage. The 3.9 kb fragments containing the light chains and pCES1 vector portion were gel purified from the total TQ library DNA. The 2.1 kb fragments 30 were ligated to the 3.9 kb fragments from the DNA sample of TQ library in 3:1 ratio. The ligated DNA was precipitated and used to transform TG1 cells by electroporation. The library size of the resulted light chain shuffled secondary library was 8.8x10<sup>8</sup>. After sequencing 96 randomly picked clones, 76 unique light chain sequences were obtained, indicating that the attempt to shuffle light chains was successful.

The binding, washing and elution condition for screening the light chain shuffle library were 35 essentially the same as described for the initial screen. However, several variations were included to increase selection pressure for amplification of IGF-1R binders with higher affinities, especially those with significantly slower off-rates. These parameters were: higher number of input phage (2-2.7 x10<sup>13</sup> pfu), smaller bead volume (100 µl for round one, 50 µl for round two, and 25 µl for round three), and extended specific elution time up to 20 hours. Elution buffers were 0.1 M TEA for round one (RD1), 1 µM IGF-1 in 40 0.4% MPBS for RD2 and 1 µM IGF-1 or IGF-2 in 0.4% MPBS for RD3. In RD2 and RD3, binders that

were eluted in 15 min or 2 hours were discarded. Elution was continued and eluted phages were collected after 8-10 hours and again after 20 hours.

#### Phage Fab ELISA Screen

5 In 96-well 2-ml deep-well blocks, 480  $\mu$ l/well 2xYT-CG broth was inoculated with 20  $\mu$ l of overnight cultures of the individual clones, then incubated at 37° C, 300 rpm for 3 hours. To each well, 50  $\mu$ l of 1:3 diluted M13KO7 helper phage were added to infect the cells. The block was incubated at 37° C without shaking for 30 minutes, and then shaken gently for another 30 minutes at 150 rpm. The block was centrifuged at 3600 rpm for 20 minutes to pellet the infected cells. The cell pellet in each well was  
10 suspended into 480  $\mu$ l of 2xYT-CK (2xYT broth containing 100  $\mu$ g/ml carbenicillin and 40  $\mu$ g/ml kanamycin), and incubated at 30° C overnight for about 20 hours. The cell debris was separated by centrifugation at 3600 rpm for 20 minutes. The rescued phage supernatant was used in the phage ELISA to check for IGF-1R-specific, INSR-cross reactive, or mouse Fc binding of individual clones.

Three sets of Nunc MaxiSorb Immunoplates were coated with 100  $\mu$ l/well of IGF-1R-C3-mFc at 5  
15  $\mu$ g/ml, INSR-mFc at 5  $\mu$ g/ml, or mouse IgG1 (catalog # 010-0103, Rockland, Gilbertsville, PA ) at 2  $\mu$ g/ml in PBS, respectively, at 4° C overnight. The coated plates were washed 3x with 300  $\mu$ l/well of PBS. The washed plates were blocked with 300  $\mu$ l/well 2% MPBS at room temperature for one hour. Meanwhile, rescued phages of individual clones were pre-blocked by mixing 170  $\mu$ l of rescued phage with 170  $\mu$ l of 4% MPBS. The blocked plates were washed 5x with 300  $\mu$ l/well TBST (TBS: 10 mM Tris-HCl, pH 7.5, 1 mM  
20 EDTA, 150 mM NaCl; Tween-20, 0.1%). 100  $\mu$ l/well of pre-blocked phage dilutions were distributed to each set of coated plate, which were incubated at room temperature on a rocker for 90 minutes. The plates were washed 5x with 300  $\mu$ l/well TBST. 100  $\mu$ l/well of anti-M13-HRP in 2% MPBS (1:3000 dilution, catalog number 27-9421-01, Amersham Pharmacia Biotech) were distributed, and plates were incubated at room temperature on rocker for one hour. The plates were washed 5x with 300  $\mu$ l/well TBST. 100  $\mu$ l/well  
25 of the substrate 1-Step™ ABTS (Pierce Biotechnology, Rockford, IL, catalog number 37615) were added. Plates were incubated for one hour. OD<sub>405</sub> was measured for signal detection.

The phage displayed antibodies exhibited essentially no crossreactivity with the insulin receptor and murine Fc domain. The signal observed in the IGF-1R ELISA is therefore specific for the IGF-1R extracellular domain. Results from similar assays for four of the phage-displayed antibodies are shown in  
30 Figure 14.

The DNA inserts of IGF-1R positive, INSR and mu IgG1 negative, clones were sequenced. Fifty-two unique Fab sequences were identified, having the following combinations of light chain and heavy chain variable domain sequences: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21,  
35 L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52, wherein "Lx" indicates light chain variable domain number "x" and "Hx" indicates heavy chain variable domain number

"x." Figure 1 presents the polynucleotide sequences of each of these light and heavy variable domains. Figures 2 and 3 present the corresponding amino acid sequences.

#### EXAMPLE 4: Subcloning of V<sub>H</sub> and V<sub>L</sub> into IgG1 expression vectors

- 5 This example presents a method of subcloning the previously identified variable domain sequences into an IgG1 expression vector.

#### Construction of pDSR $\alpha$ 20 and pDSR $\alpha$ 20:hIgG1C<sub>H</sub>

- 10 The pDSR $\alpha$ 20:hIgG1C<sub>H</sub> expression vector (WO 90/14363) was a derivative of pDSR19:hIgG1C<sub>H</sub> (see U.S. Provisional Patent Application No. 60/370,407, filed April 5, 2002, "Human Anti-OPGL Neutralizing Antibodies As Selective OPGL Pathway Inhibitors," incorporated herein by reference in its entirety). The pDSR $\alpha$ 19:hIgG1C<sub>H</sub> plasmid encoded a rat variable region/human constant region IgG1 (rVh/hCh1). The plasmid was constructed by the three-piece ligation of *Xba* I and *BsmB* I terminated rat antibody variable region PCR product, the human IgG1 constant region (C<sub>H1</sub>, hinge, C<sub>H2</sub> and C<sub>H3</sub> domains) derived by *Sal* I cleavage and gel isolation of the *BsmB* I and *Sal* I fragment from the linear plasmid pDSR $\alpha$ 19:hIgG1 C<sub>H</sub> (*Hind* III and *BsmB* I ends) and a linearized pDSR $\alpha$ 19 with *Xba* I and *Sal* I ends.
- 15 pDSR $\alpha$ 20 was produced by changing nucleotide 2563 in pDSR $\alpha$ 19 from a guanosine to an adenosine by site directed mutagenesis. The heavy chain expression vector, pDSR $\alpha$ 20:hIgG1C<sub>H</sub> rat variable region/human constant region IgG1 (rVh/hCh1), is 6163 base pairs and contains the 7 functional regions described in Table 3.
- 20

Table 3

#### Plasmid Base

#### Pair Number:

25

2 to 881	A transcription termination/polyadenylation signal from the $\alpha$ -subunit of the bovine pituitary glycoprotein hormone ( $\alpha$ -FSH) (Goodwin <i>et al.</i> , 1983, <i>Nucleic Acids Res.</i> 11:6873-82; Genbank Accession Number X00004)
882 to 2027	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser <i>et al.</i> , 1982, <i>Proc. Natl. Acad. Sci. U. S. A.</i> 79:6522-6; Nunberg <i>et al.</i> , 1980, <i>Cell</i> 19:355-64; Setzer <i>et al.</i> , 1982, <i>J. Biol. Chem.</i> 257:5143-7; McGrogan <i>et al.</i> , 1985, <i>J. Biol. Chem.</i> 260:2307-14)
2031 to 3947	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in <i>E. coli</i> (Genbank Accession Number J01749)
3949 to 4292	An SV40 early promoter, enhancer and origin of replication (Takebe <i>et al.</i> , 1988, <i>Mol. Cell Biol.</i> 8:466-72, Genbank Accession Number J02400)
4299 to 4565	A translational enhancer element from the HTLV-1 LTR domain (Seiki <i>et al.</i> , 1983, <i>Proc. Natl. Acad. Sci. U. S. A.</i> 80:3618-22, Genbank Accession Number J02029)
4574 to 4730	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983, <i>Mol. Cell Biol.</i> 3:280-9, Genbank Accession Number J02400)
4755 to 6158	The rVh/hCh1 heavy chain cDNA between the <i>Xba</i> I and <i>Sal</i> I sites. This heavy chain fragment sequence is shown below (SEQ ID NO: 262) with the sequences of the restriction sites underlined: <i>Xba</i> I TCTAG ACCACCATGG ACATCAGGCT CAGCTTAGTT TTCCTTGTC

	<p>TTTTCATAAA AGGTGTCCAG TGTGAGGTAG AACTGGTGGA  GTCTGGGGGC GGCTTAGTAC AACCTGGAAG GTCCATGACA  CTCTCCTGTG CAGCCTCGGG ATTCACITTC AGAACCTATG GCATGGCCTG  GGTCCGCCAG GCCCCAACGA AGGGTCTGGA GTGGGTCTCA  TCAATTACTG CTAGTGGTGG TACCACCTAC TATCGAGACT CCGTGAAGGG  CCGCTTCACT ATTTTATAGG ATAATGCAAA AAGTACCCTA TACCTGCAGA  TGGACAGTCC GAGGTCTGAG GACACGGCCA CTTATTCTG TACATCAATT  TCGGAATACT GGGGCCACGG AGTCATGGTC</p> <p><i>BsmB1</i>  ACCGTCTCTA GTGCCTCCAC CAAGGGCCCCA TCGGTCTTCC CCCTGGCACC  CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC  TGCCTGGTCA AGGACTACTT CCCC GAACCG GTGACGGTGT  CGTGGAATC AGGCGCCCTG ACCAGCGGCG TGCACACCTT  CCCGGCTGTC CTACAGTCCT CAGGACTCTA CTCCTCAGC AGCGTGGTGA  CCGTGCCCTC CAGCAGCTTG GGCACCCAGA CCTACATCTG  CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG  AAAGTTGAGC CCAAATCTTG TGACAAAAC CACACATGCC  CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCTCTTC  CCCCAAAAC CCAAGGACAC CCTCATGATC TCCCGGACCC  CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA  CCCTGAGGTC AAGTTCAACT GGTACGTGGA CGGCGTGGAG  GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA  ACAGCACGTA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA  CCAGGACTGG CTGAATGGCA AGGAGTACAA GTGCAAGGTC  TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT  CCAAAGCCAA AGGGCAGCCC CGAGAACCAC AGGTGTACAC  CCTGCCCCCA TCCCGGGATG AGCTGACCAA GAACCAGGTC  AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA  TCGCCGTGGA GTGGGAGAGC AATGGGCAGC CGGAGAACAA  CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT  ATAGCAAGCT CACCGTGGAC AAGAGCAGGT GGCAGCAGGG  GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCCTACA  CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA</p> <p><i>SalI</i>  AATGATAAGT CGAC</p>
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The linear plasmid pDSR $\alpha$ 20:hIgG1C<sub>H</sub> was prepared by digesting the pDSR20: rat variable region/human constant region IgG1 plasmid with the restriction enzymes *Xba* I and *BsmB* I to remove the rat variable region and purified using a QIAquick Gel Extraction kit. The linear plasmid

5 pDSR $\alpha$ 20:hIgG1C<sub>H</sub> containing the 1.0 kbp human IgG1 constant region domain was used to accept anti-IGF-1R variable heavy chain coding sequences.

#### Construction of the anti-IGF-1R IgG1 Heavy Chain Expression Clones

The sequence coding for the anti-IGF-1R variable region of the heavy chains was amplified from

10 phagemid DNA with complementary oligonucleotide primers. Primers for polymerase chain reaction (PCR) were designed to incorporate a *Hind* III site, *Xba* I site, Kozak sequence (CCACC) and signal sequence (translated peptide is MDMRVPAQLLGLLLWLRGARC; SEQ ID NO:263) onto the 5' end of the variable region, while a *BsmB* I site was added onto the 3' end of the PCR product. The PCR products were digested with *Xba* I and *BsmB* I, and then cloned into the *Xba* I-*BsmB* I linear pDSR $\alpha$ 20:hIgG1C<sub>H</sub>

15 expression vector containing the human IgG1 constant region (Figure 13). The final expression vectors contained the seven functional regions described in Table 4.

Table 4

Plasmid BasePair Number:

2 to 881	A transcription termination/polyadenylation signal from the $\alpha$ -subunit of the bovine pituitary glycoprotein hormone ( $\alpha$ -FSH) (Goodwin <i>et al.</i> , 1983, <i>Nucleic Acids Res.</i> <u>11</u> :6873-82; Genbank Accession Number X00004)
882 to 2027	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser <i>et al.</i> , 1982, <i>Proc. Natl. Acad. Sci. U. S. A.</i> <u>79</u> :6522-6; Nunberg <i>et al.</i> , 1980, <i>Cell</i> <u>19</u> :355-64; Setzer <i>et al.</i> , 1982, <i>J. Biol. Chem.</i> <u>257</u> :5143-7; McGrogan <i>et al.</i> , 1985, <i>J. Biol. Chem.</i> <u>260</u> :2307-14)
2031 to 3947	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in <i>E. coli</i> (Genbank Accession Number J01749)
3949 to 4292	An SV40 early promoter, enhancer and origin of replication (Takebe <i>et al.</i> , 1988, <i>Mol. Cell Biol.</i> <u>8</u> :466-72, Genbank Accession Number J02400)
4299 to 4565	A translational enhancer element from the HTLV-1 LTR domain (Seiki <i>et al.</i> , 1983, <i>Proc. Natl. Acad. Sci. U. S. A.</i> <u>80</u> :3618-22, Genbank Accession Number J02029)
4574 to 4730	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983, <i>Mol. Cell Biol.</i> <u>3</u> :280-9, Genbank Accession Number J02400)
4755 to 6185	The heavy chain IgG1 cDNA between the <i>Xba</i> I and <i>Sal</i> I sites

5

Construction of the anti-IGF-1R IgG1 Variable Chain Expression Clones.

The light chains encoded in anti-IGF-1R phage were either kappa or lambda class. They were cloned using one of two approaches. Complementary primers were designed to add a *Hind* III site, an *Xba* I site, Kozak sequence (CCACC) and signal sequence (translated peptide is

- 10 MDMRVPAQLLGLLLLWLRGARC, SEQ ID NO:264) were added to the 5' end of the coding region. Those chains that had error-free coding regions were cloned as full-length products. The full-length light chains were cloned as *Xba* I and *Sal* I fragments into the expression vector pDSR $\alpha$ 20. The final expression vectors contained the seven functional regions described in Table 5.

15 Table 5

Plasmid BasePair Number:

2 to 881	A transcription termination/polyadenylation signal from the $\alpha$ -subunit of the bovine pituitary glycoprotein hormone ( $\alpha$ -FSH) (Goodwin <i>et al.</i> , 1983, <i>Nucleic Acids Res.</i> <u>11</u> :6873-82; Genbank Accession Number X00004)
882 to 2027	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser <i>et al.</i> , 1982, <i>Proc. Natl. Acad. Sci. U. S. A.</i> <u>79</u> :6522-6; Nunberg <i>et al.</i> , 1980, <i>Cell</i> <u>19</u> :355-64; Setzer <i>et al.</i> , 1982, <i>J. Biol. Chem.</i> <u>257</u> :5143-7; McGrogan <i>et al.</i> , 1985, <i>J. Biol. Chem.</i> <u>260</u> :2307-14)
2031 to 3947	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in <i>E. coli</i> (Genbank Accession Number J01749)
3949 to 4292	An SV40 early promoter, enhancer and origin of replication (Takebe <i>et al.</i> , 1988, <i>Mol. Cell Biol.</i> <u>8</u> :466-72, Genbank Accession Number J02400)
4299 to 4565	A translational enhancer element from the HTLV-1 LTR domain (Seiki <i>et al.</i> , 1983, <i>Proc. Natl. Acad. Sci. U. S. A.</i> <u>80</u> :3618-22, Genbank Accession Number J02029)



4574 to 4730	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983, <i>Mol. Cell Biol.</i> 3:280-9, Genbank Accession Number J02400)
4755 to 5485	The kappa light chain cDNA between the <i>Xba</i> I and <i>Sal</i> I sites

Some kappa clones had errors in their constant regions when compared to natural human constant region sequence. To eliminate these discrepancies, the kappa variable region was amplified with a primer that would introduce an *Xba* I site into the 5' end and a *BsmB* I site into the 3' end. This fragment was then ligated along with a human kappa constant region (Figure 13) with a compatible *BsmB* I on the 5' end and a 3'*Sal* I ends into pDSR $\alpha$ 20 with *Xba* I and *Sal* I ends.

#### EXAMPLE 5: Transient Expression of Antibodies

This example provides a method of transiently expressing anti-IGF-1R antibodies.

The antibodies were expressed transiently in serum-free suspension adapted 293T cells. All transfections were performed as 250 mL cultures. Briefly,  $1.25 \times 10^8$  cells ( $5.0 \times 10^5$  cells/mL  $\times$  250 mL) were centrifuged at 2,500 RPM for 10 minutes at 4° C to remove the conditioned medium. The cells were resuspended in serum-free DMEM and centrifuged again at 2,500 RPM for 10 minutes at 4° C. After aspirating the wash solution, the cells were resuspended in growth medium [DMEM/F12 (3:1) + 1x Insulin-Transferrin-Selenium Supplement + 1X Pen Strep Glut + 2mM L-Glutamine + 20 mM HEPES + 0.01% Pluronic F68] in a 500 mL spinner flask culture. The spinner flask culture was maintained on magnetic stir plate at 125 RPM which was placed in a humidified incubator maintained at 37° C and 5% CO<sub>2</sub>. The plasmid DNA was incubated with the transfection reagent in a 50 mL conical tube. The DNA-transfection reagent complex was prepared in 5% of the final culture volume in serum-free DMEM. One microgram of plasmid DNA per milliliter of culture was first added to serum-free DMEM, followed by 1  $\mu$ l X-TremeGene RO-1539/mL culture. The complexes were incubated at room temperature for approximately 30 minutes and then added to the cells in the spinner flask. The transfection/expression was performed for 7 days, after which the conditioned medium was harvested by centrifugation at 4,000 RPM for 60 minutes at 4° C.

If the initial transfection failed to yield the required 100  $\mu$ g purified antibody, those clones were re-expressed in roller bottles. These transfections used 293T adherent cells grown and maintained in DMEM supplemented with 5% FBS + 1x Non-Essential Amino Acids + 1x Pen Strep Glut + 1x Sodium Pyruvate. Approximately,  $4-5 \times 10^7$  293T cells were seeded in a 850 cm<sup>2</sup> roller bottles overnight. The previously seeded cells were then transfected the following day using FUGENE<sup>TM</sup> 6 transfection reagent. The DNA – transfection reagent mixture was prepared in approximately in 6.75 mL serum-free DMEM. 675  $\mu$ l FUGENE<sup>TM</sup> 6 transfection reagent was first added, followed by 112.5  $\mu$ g plasmid DNA. The complex was incubated at room temperature for 30 minutes. The entire mixture was then added to a roller bottle. The roller bottle was infused with a 5% CO<sub>2</sub> gas mixture, capped tightly and placed in a 37° C incubator on a roller rack rotating at 0.35 RPM. The transfection was performed for 24 hours after which the medium was replaced with 100 mL DMEM + 1X Insulin-Transferrin-Selenium Supplement + 1X Pen Strep Glu + 1X Non-Essential Amino Acids + 1X Sodium Pyruvate. Typically, 2-3 harvests (100ml) were obtained from each roller bottle at a 48 hr interval. The harvested serum-free conditioned medium was pooled together and centrifuged at 4,000 RPM for 30 minutes at 4° C.

**EXAMPLE 6: Anti-IGF-1R Antibody Small-scale Purification**

This example provides a method of purifying anti-IGF-1R antibodies on a small scale.

Conditioned medium was filtered through a 0.45 µm cellulose acetate filter and concentrated approximately 8-fold using a Vivaflow 200 50 K tangential flow membrane (Vivascience, Goettingen, Germany). rProtein A SEPHAROSE™ Fast Flow resin (Amersham Biosciences, Piscataway, NJ) was washed with phosphate buffered saline (2.7 mM potassium chloride, 138 mM sodium chloride, 1.5 mM potassium phosphate, and 8.1 mM sodium phosphate, pH 7.4) (PBS) four times then directly applied to the concentrated media. The amount of resin used was based on antibody concentration determined by ELISA where 1 µl of resin was used per 5 µg antibody. The medium was incubated overnight at 4° C with gentle agitation. The resin was centrifuged at 500 g for 10 min. at 4° C. The supernatant was decanted as the unbound fraction. The resin was washed with PBS four times for one minute at room temperature with gentle agitation, each time collecting the resin by centrifugation at 500 g for 10 min. at 4° C. The antibody was eluted by incubating the resin with 1.5 volumes of 0.1 M glycine pH 3.0 for 10 min. at room temperature. The resin was centrifuged at 500 g for 10 min. at 4° C and the supernatant decanted as eluted antibody. The elution step described above was repeated for a total of three elutions; each time the eluted material was neutralized with 0.04 volumes of 1.0 M tris-HCl, pH 9.2. The sample was filtered through a 0.2 µm cellulose acetate filter. Protein concentration was determined by the Bradford method using the Bio-Rad Protein Assay (Bio-Rad Laboratories, Hercules, CA) as per the supplied instructions using Human IgG (Sigma-Aldrich, St. Louis, MO) as a standard. The sample was compared to a Human IgG1, K standard (Sigma-Aldrich, St. Louis, MO) using a 4-20% tris-glycine SDS polyacrylamide gel (SDS-PAGE) gel stained with Coomassie brilliant blue dye. No contaminating protein was visible in these preparations.

**EXAMPLE 7: Isolation of Stable CHO Clones Expressing Antibodies**

This example provides a method for isolating stable CHO cell lines expressing anti-IGF-1R antibodies.

Stable expression of TQ11C, TQ25, TQ 58 and TQ59 IgG1 was achieved by co-transfection of AM1-D CHO cells (U.S. Pat. No. 6,210,924, incorporated herein by reference in its entirety) with pDSRα20 heavy and light chain IgG1 expression constructs. The plasmid transfections were performed using LF2000 (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Briefly, 4 x 10<sup>6</sup> AM1-D CHO cells were plated 24 hours prior to transfection, in 100 mm diameter FALCON™ plastic petri dishes (BD Falcon, Franklin Lakes, NJ) in 10 ml of Dulbecco's Modified Eagles Medium (Invitrogen) supplemented with 5% fetal bovine serum, 1x penicillin-streptomycin and glutamine (Invitrogen), non-essential amino acids (Invitrogen), sodium pyruvate, and HT (0.1 mM sodiumhypoxanthine, 16 nM thymidine; Invitrogen). Approximately 15 mg of each pDSRα21 - light chain and heavy chain plasmid DNA were linearized using *Pvu* I (New England Biolabs) and diluted in 2 ml of OPTI-MEM® (Invitrogen). The diluted plasmids were mixed with 75 µl of LIPOFECTAMINE™ 2000 (LF2000; GIBCO/BRL) diluted in 2 ml of OPTI-MEM® and the mixture was incubated for 20 min at room temperature. The following day fresh growth medium was added. The cells were cultured in complete growth medium for 48 hours, then plated in HT- selection medium in 1:20 and 1:50 dilutions. Approximately 2 weeks after transfection, 12-24 visible colonies were picked into 24-well plates, using the sterile cloning discs (RPI). The clones

expressing the highest level of TQ11C, TQ25, TQ58 and TQ59 IgG1 were identified by western immunoblot analysis. To perform this assay, 0.5 ml of serum free medium was added to a single-well confluent cells cultured in a 24 well plate (BD Falcon). The conditioned medium was recovered after 24 hr, and 10 µl of CM was mixed with an equal volume of loading buffer to run a 10% Tris-Glycine polyacrylamide protein gel (Invitrogen). The gel was transferred to a 0.45 µm pore size nitrocellulose membrane (Invitrogen), and western blot analysis was done using 1:1000 dilution of goat anti-human IgG Fc ImmunoPure antibody (Pierce Biotechnology, Inc., Rockford, IL) and ECL as detection agent.

#### EXAMPLE 8: Mid-scale Expression of Antibodies

This example provides a method of expressing anti IGF-1R antibodies expressed by stable CHO cell lines.

The CHO cell lines made according to Example 7 were expanded to T-175 tissue culture flasks (Falcon) for scale-up expression. A confluent T175 flask (approximately  $2-3 \times 10^7$  cells) was used to seed 3 - 850 cm<sup>2</sup> roller bottles (Corning Life Sciences, Acton, MA), and three confluent roller bottles (approximately  $1-2 \times 10^8$  cells per roller bottle) were used to seed 30 rollers in 250 ml of high-glucose DMEM (Invitrogen), 10% dialyzed FBS (Invitrogen), 1x glutamine (Invitrogen), 1x non-essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen). Medium was infused with 10% CO<sub>2</sub>/balance air for 5 seconds before capping the roller bottle. Roller bottles were incubated at 37° C on roller racks spinning at 0.75 rpm.

When cells reached approximately 85-90% confluency (approximately 5-6 days in culture), the growth medium was discarded, the cells were washed with 100 ml PBS, and 200 ml production medium was added (50% DMEM (Invitrogen)/ 50% F12 (Invitrogen), 1x glutamine (Invitrogen), 1x non-essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen), 1.5% DMSO (Sigma). Conditioned medium was harvested every seven days for a total of four harvests.

Conditioned medium was filtered through a 0.45 µm cellulose acetate filter and concentrated approximately 10-fold using a Sartorius Sartocon Slice Disposable 30 K tangential flow membrane (Sartorius AG, Goettingen, Germany). The concentrated material was applied to a 10 ml rProtein A Sepharose column at 4° C and the flowthrough was collected as the unbound fraction. The column was washed with four column volumes of PBS. The bound sample was eluted with approximately four column volumes of 0.1 M glycine pH 3.0. The eluate peak was collected and neutralized with 0.04 volumes of 1.0 M tris-HCl, pH 9.2. The eluate was dialyzed against 150 volumes of PBS overnight at 4° C. The sample was filtered through a 0.2 µm cellulose acetate filter and protein concentration was measured by determining the absorbance at 280nm using an extinction coefficient of 14,000 M<sup>-1</sup>. The sample was compared to a Human IgG1, K standard (Sigma-Aldrich, St. Louis, Missouri, USA) using a 4-20% tris-glycine SDS-PAGE gel stained with Coomassie brilliant blue stain. Endotoxin levels in each antibody preparation was determined using the Pyrotell Limulus Amebocyte Lysate Assay (Associates of Cape Cod, Inc., Falmouth, Ma) as per the supplied instructions.

#### EXAMPLE 9: ORIGEN® Dose Response Competition Assays

This example provides methods for testing the ability of an antibody to block ligand binding to IGF-1R.

An ORIGEN<sup>®</sup> binding assay was used to determine whether TQ11C, TQ25, TQ 58 and TQ59 IgG1 antibodies could block ligand binding to IGF-1R using procedures provided by the manufacturer (Igen, Inc., Gaithersburg, MD). To label IGF-1 and IGF-2 with ruthenium, lyophilized proteins were dissolved into PBS to give a 1.0 mg/ml solution. Label (ORI-TAG-NHS ester from Igen, Cat # 110034) was added to the protein at a molar ratio of 5:1 (label: protein) from a label stock of 5 mg/ml in DMSO. The mixture was incubated at room temperature (20-22° C) for 1 hr in the dark then treated with 20  $\mu$ l 2M glycine for 10 min at room temperature. The labeled protein was separated from the free label by application to an Amersham Biosciences NAP-5 column (Amersham Biosciences, Piscataway, NJ) equilibrated in PBS and 0.33 ml fractions collected. The protein concentration of the fractions was determined by Micro BCA Protein Assay (Pierce Biotechnology, Inc., Rockford, IL). Fractions two and three contained significant protein and were combined. The amount of incorporated ruthenium label was assessed using the following formula: ruthenium tris-bipyridyl compound ( $\text{Ru}(\text{bpy})_3^{2+}$ ) labeling of IGF-1 and IGF-2.

Dynal M450 paramagnetic beads coated with sheep anti-mouse IgG was used as the solid support phase for the IGF-1R(ECD)-C3-muFc. The M450 beads were prepared for receptor loading by washing three times with assay buffer containing 1x PBS, 0.05% TWEEN<sup>™</sup> 20 (ICI Americas, Inc., Wilmington DE) 0.1% BSA, 0.01% sodium azide. The IGF-1R(ECD)-C3-muFc was bound for 1 hr at a ratio of 50 ng receptor per  $1 \times 10^6$  M450 beads in a volume of 25  $\mu$ l assay buffer. To generate dose response data, the antibodies or unlabeled IGF-1 and IGF-2 factors were added at increasing concentrations ( $10^{-11}$ M to  $10^{-6}$ M) simultaneously with 1 nM Ru-IGF-1 or 2 nM Ru-IGF-2. The final reaction volume was 100  $\mu$ l. After incubation at room temperature in the dark for 2 hr, an M8 Analyzer (Igen) was used to remove free ruthenium labeled ligand and determine the amount of ligand bound to receptor. The data were expressed as the percent of total ligand bound minus background remaining after competition with excess unlabeled growth IGF1 or IGF-2. Competition curves were generated with GraphPad Prism software (GraphPad Software, San Diego, CA) using a single component equilibrium model. Essentially all (> 98%) binding was competed with excess unlabeled growth factors. The positive control antibodies in the binding analysis were the murine anti-IGF-1R antibodies  $\alpha$ IR3 (Calbiochem, San Diego, CA) or MAB391 (R&D systems, Minneapolis, MN), 24-57 (Biocarta, San Diego, CA) and 1H7 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA). The negative control antibody was an anti-CD20 antibody. Ligand competition data are shown in Figure 15. The  $K_i$  and maximum inhibition values observed for IGF-1 and IGF-2 binding reactions are listed in Table 6.

Table 6

Antibody	IGF-1		IGF-2	
	$K_i$ (nM) <sup>1</sup>	Max (%) <sup>2</sup>	$K_i$ (nM) <sup>1</sup>	Max (%) <sup>2</sup>
TQ11C	0.6	84	0.3	91
TQ25	0.8	88	0.8	94

TQ58	0.8	91	0.8	91
TQ59	1.5	79	1.4	91
1H7	16.0	89	13.1	99
$\alpha$ IR3	5.3	91	No Inhibition	

<sup>1</sup> Ki of inhibition.

<sup>2</sup> Maximum level of inhibition at 1  $\mu$ M antibody concentration.

#### 5 EXAMPLE 10: SPA Dose Response Competition Assay

This example presents a scintillation proximity assay (SPA) for assessing the effect of antibodies on the interaction of insulin (INS) with the insulin receptor (INSR) and of IGF-1 and IGF-2 to IGF-1R.

IGF-1R binding reactions for TQ11C, TQ25, TQ 58 and TQ59 IgG1 antibodies contained 1x PBS, 0.05% TWEEN® 20 (Mallinkrodt), 0.1% BSA (EM Science, Gibbstown, NJ), 50 ng IGF-1R(ECD)-C3-muFc, 500 ug SPA PVT anti-mouse IgG fluoromicrospheres (Amersham) and <sup>125</sup>I-labeled IGF-1 or IGF-2 obtained from Amersham at a final concentration of 0.64 nM. The total reaction volume was 100  $\mu$ l. The INSR binding reactions were identical except they contained 50 ng INSR(ECD)-muFc and 0.64 nM <sup>125</sup>I-INS (Amersham). Receptor was loaded onto SPA PVT microspheres for 1h at room temperature prior to assembly of the binding reactions. To generate dose response data, antibodies or unlabeled growth factors were added at increasing concentrations (10<sup>-11</sup> M to 10<sup>-6</sup> M) simultaneously with <sup>125</sup>I-labeled growth factors. Essentially all binding was competed with excess unlabeled growth factors. The receptor-independent background, caused by random  $\gamma$  stimulation of the SPT PVT microspheres, was less than 0.5% of the input <sup>125</sup>I cpm. The data were expressed as the percent of total ligand bound minus background remaining after competition with excess unlabeled growth IGF1 or IGF-2. Competition curves were generated with GraphPad Prism software using a single component equilibrium model.

#### EXAMPLE 11: Antibody Binding to IGF-1R

This example provides a method of detecting the binding of an anti-IGF-1R antibody to IGF-1R.

BIACORE® 2000, sensor chip CM5, surfactant P20, HBS-EP (10mM HEPES, 0.15M NaCl, 3.4mM EDTA, 0.005% P20, pH 7.4), amine coupling kit, 10mM acetate pH 4.5 and 10mM glycine pH 1.5 all were purchased from BIAcore, Inc. (Piscataway, NJ). Phosphate-buffered saline (PBS, 1X, no calcium chloride, no magnesium chloride) was from Gibco. Bovine serum albumin (BSA, fraction V, IgG free) was from Sigma. Recombinant Protein G ("rProtein G") was from Pierce Biotechnology.

Immobilization of rProtein G and IGF-1R-C3-muFc to the sensor chip surface was performed according to manufacturer's instructions, using a continuous flow of 10mM HEPES, 0.15M NaCl, 3.4mM EDTA, 0.005% P20, pH 7.4 (HBS-EP buffer). Briefly, carboxyl groups on the sensor chips's surfaces were activated by injecting 60  $\mu$ l of a mixture containing 0.2 M N-ethyl-N'-(dimethylaminopropyl)carbodiimide (EDC) and 0.05 M N-hydroxysuccinimide (NHS). Specific surfaces were obtained by injecting rProtein A (Pierce) or IGF-1R-C3-mFc diluted in 10mM acetate, pH 4.5 at concentrations between 20 and 50  $\mu$ g/ml. Excess reactive groups on the surfaces were deactivated by injecting 60  $\mu$ l of 1 M ethanolamine. Final immobilized levels were 5,000-6,000 resonance units (RU) for the Protein G surfaces, and ~7,800 RU for

the IGF-1R-mFc surfaces. A blank, mock-coupled reference surface was also prepared on the IGF-1R-mFc sensor chip.

The kinetic analysis of the interaction between IGF-1R-mFc and antibodies was performed as follows. Antibodies as well as a positive control antibody (anti-IR3-CDR-human-mouse chimera) were diluted in PBS + 0.005% P20 + 0.1 mg/ml BSA and injected over the Protein G surfaces to capture the antibodies. IGF-1R-mFc was diluted in PBS + 0.005% P20 + 0.1 mg/ml BSA from 500nM to 3.9nM, and each concentration was injected over the captured antibody surfaces, as well as over a blank Protein G surface for background subtraction. After a 10 minute dissociation, each surface was regenerated by injecting 10mM glycine, pH 1.5. Kinetic analysis of the resulting sensorgrams was performed using BIAEvaluation, v. 3.2 (BIAcore, Inc.).

A solution affinity analysis was done by incubating two different concentrations (0.2nM and 1nM) of antibody with varying concentrations (0.01nM to 50nM) of IGF-1R-mFc in PBS + 0.005% P-20 + 0.1 mg/ml BSA. Incubations were done at room temperature for at least five hours to allow samples to reach equilibrium. Samples were then injected over the immobilized IGF-1R-mFc surface. After the sample injection, the surfaces were regenerated by injecting 25  $\mu$ l 8mM glycine, pH 1.5. The binding signal obtained is proportional to the free antibody in solution at equilibrium. The dissociation equilibrium constant ( $K_D$ ) was obtained from nonlinear regression analysis of the competition curves using a dual-curve one-site homogeneous binding model (KinExA software v. 2.3, Savidyne Instruments Inc., Boise ID). The data are shown in Table 7

Table 7

Antibody	$k_{on}$ (1/Ms)	$K_d$ (1/s)	$K_d$ ( $k_a/k_d$ ) Kinetic Method	$K_d$ Equilibrium Method
TQ11C	$6.0 \times 10^4$	$6.7 \times 10^{-5}$	1.1 nM	0.3 nM
TQ25	$4.4 \times 10^4$	$<<5 \times 10^{-5}$		0.10 nM
TQ58	$1.1 \times 10^5$	$2.8 \times 10^{-5}$	0.25 nM	0.25 nM
TQ59	$6.9 \times 10^4$	$2.1 \times 10^{-4}$	3.0 nM	0.30 nM

#### EXAMPLE 12: Epitope Mapping Avidin-Fusion proteins

This example provides a method of determining the epitope of IGF-1R bound by an anti-IGF-1R antibody.

The subdomains of IGF-1R bound by antibodies TQ11C, TQ25, TQ58, and TQ59 were determined using avidin-IGF-1R fusion proteins. To express each protein the coding DNA sequences of the complete IGF-1R(ECD) was cloned into the expression vector pCep4-avidin-C such that chicken avidin sequence is joined to the C-terminus of the expressed IGF-1R protein. The ECD coding sequence (1-932) was PCR amplified from a parental IGF-1R plasmid using PCR primers 2804-25:

5' GCAAGCTTGGGAGAAATCTGCGGGCCAG 3' SEQ ID NO:265

and 2826-68:

5' ATTGCGGCCGCTTCATATCCTGTTTTGGCCTG 3' SEQ ID NO:266

The primers include a 5' *Hind* III site and a 3' *Not* I site for cloning into pCep4avidin-C. The amino acid sequence of the avidin-human IGF-1R(ECD) fusion protein is shown in Figure 12. The IGF-1R subdomains constructs used for epitope mapping included: L1 (1-151), CR (152-298), L2 (299-461), FnIII-1 (461-579), FnIII-2/ID (580-798), FnIII-3 (799-901), L1+CR+L2 (1-461), and L1+CR (1-298). The amino acid coordinates of the IGF-1R subdomain represented in each expression plasmid are given in parenthesis. The coding sequence of each domain was PCR amplified from a parental IGF1R cDNA clone using the following primer pairs:

L1:

2804-25: (SEQ ID NO:265)

2804-19:

5' ATTGCGGCCGCCCCACATTCCTTTGGGGGC 3' SEQ ID NO:267

CR:

2804-38:

5' AGCAAGCTTGGACCTGTGTCCAGGGACC 3' SEQ ID NO:268

2804-20:

5' ATTGCGGCCGCGCAAGGACCTTCACAAGGG 3' SEQ ID NO:269

L2:

2804-39:

5' AGCAAGCTTGCCGAAGGTCTGTGAGGAAG 3' SEQ ID NO:270

2804-23:

5' ATTGCGGCCGCACTTTTCACAGGAGGCTCTC 3' SEQ ID NO:271

FnIII-1:

2808-08:

5' AGCAAGCTTGGACGTCCTGCATTTTCACCTC 3' SEQ ID NO:272

2804-52:

5' ATTGCGGCCGCGGTGCGAATGTACAAGATCTC 3' SEQ ID NO:273

FnIII-2+ID:

2804-41:

5' AGCAAGCTTGAATGCTTCAGTTCCTTCCATTC 3' SEQ ID NO:274

2804-51:

5' ATTGCGGCCGCGAGTCCTTGCAAAGACGAAGTTG 3' SEQ ID NO:275

FnIII-3:

2804-42:

5' AGCAAGCTTGATGCCCCGAGAAGGAGCAG 3' SEQ ID NO:276

2804-50:

5' ATTGCGGCCGCTTTAATGGCCACTCTGGTTTC 3' SEQ ID NO:277

L1+CR+L2:

2804-25:

5' AGCAAGCTTGGGAGAAATCTGCGGGCCAG 3' SEQ ID NO:278

2804-23 (SEQ ID NO:272)

L1+CR:

2804-25: AGC AAG CTT GGG AGA AAT CTG CGG GCC AG (SEQ ID NO:279)

2804-20 (SEQ ID NO:270)

The primers included *Hind* III and *Not* I site for cloning as described for the IGF-1R (ECD). The IGF-1R subdomains were cloned into the expression vector pCep4avidin-N such that chicken avidin sequence (with endogenous signal sequence) is joined to the N-terminus of the expressed IGF-1R proteins.

5 Expression of each avidin-fusion protein was achieved by transient transfection of human 293-EBNA cells (Invitrogen) in roller bottles cultures. The cells were grown and maintained in DMEM supplemented with 5% FBS + 1x Non-Essential Amino Acids + 1x Pen Strep Glut + 1x Sodium Pyruvate. Approximately 4-5 x 10<sup>7</sup> 293-EBNA cells were seeded in 850 cm<sup>2</sup> roller bottles overnight. The previously seeded cells were then transfected with pCep4-avidin plasmid DNA the following day using FUGENE<sup>TM</sup> 6 transfection

10 reagent. The DNA-transfection reagent mixture was prepared in approximately in 6.75 mL serum-free DMEM. 675 µl FUGENE<sup>TM</sup> 6 transfection reagent was first added, followed by 112.5 µg plasmid DNA. The complex was incubated at room temperature for 30 minutes. The entire mixture was then added to a roller bottle. The roller bottle was gassed with a 5% CO<sub>2</sub> gas mixture, capped tightly and placed in a 37° C incubator on a roller rack rotating at 0.35 RPM. The transfection was performed for 24 hours after which

15 the medium was replaced with 100 mL DMEM + 1X Insulin-Transferrin-Selenium Supplement + 1X Pen Strep Glu + 1X Non-Essential Amino Acids + 1X Sodium Pyruvate. Harvest of the condition medium and replacement with fresh medium occurred 48 hr intervals (2-3 cycles). The harvested serum-free conditioned medium was pooled together and clarified by centrifugation at 10,000 x g for 30 minutes at 4° C.

20 The concentration of avidin-fusion in each conditioned medium was determined using a quantitative FACS based method. The avidin fusion protein in 200 µl of conditioned medium was captured by incubation for 2 hr at room temperature with 5 µl (~ 3.5 x 10<sup>5</sup>) of biotin coated polystyrene beads (Spherotech, Inc., Libertyville, IL). The conditioned medium was removed by three cycles of centrifugation and resuspension of the avidin-coated beads in PBS containing 0.5% BSA (BPBS). The

25 avidin-beads were stained with 1 µg/ml of goat FITC-labeled anti-avidin antibody (Vector Lab Burlingame, CA) in 1ml BPBS. After 0.5 hr incubation antibody-beads complexes were collected by centrifugation at 1800 rpm for 5 min and the pellet was washed three times. The FITC fluorescence was detected with a FACSCAN (Beckton Dickson Bioscience, Franklin Lakes, NJ). The signal was converted to protein mass using a standard curve derived with recombinant avidin. For epitope mapping the biotin-beads were loaded

30 with 50-100 ng avidin-fusion protein per ~3.5 x 10<sup>5</sup> beads of beads by incubation with the appropriate amount (1-20 ml) of conditioned medium. The loaded beads were washed extensively and resuspended in 1ml BPBS. For all experiment the biotin-beads were blocked with 10% BSA in PBS prior to loading fusion protein.

*Method 1, One Color Assay:* Biotin-coated polystyrene beads loaded with IGF-1R (ECD) and

35 IGF-1R subdomain fusion proteins were mixed with 1 µg of anti-IGF-1R antibody in 1 ml of BPBS. After incubation for 1 hr at room temperature, 4 ml washing buffer was added and the antibody-beads complexes were collected by centrifugation for 5 min at 750g. The pellet was washed 3 times by resuspension in 4 ml of BPBS. The antibody bound to avidin-bead complexes was detected by treatment with 0.5 µg/ml Phycoerythrin-(PE) labeled goat anti-human F(ab')<sub>2</sub> (Southern Biotech Associates, Inc., Birmingham, AL)

40 in 1 ml BPBS. Tested antibodies were found to bind to the avidin-fusion protein containing the complete



IGF-1R ECD and the L2 domain. Binding to L1, CR or FnIII-1 was not detected in this experiment. A relatively weak reaction was also observed with the L1 domain.

*Method 2, Two color assay:* To simultaneously monitor the amounts of anti-IGF-1R monoclonal antibody and avidin-fusion bound to biotin-beads, FITC-labeled anti-avidin antibody was included (1 µg/ml) was included in the binding reaction in combination with 0.5 µg/ml PE-labeled goat anti-human IgG1. The beads were prepared for FACSCAN analysis as described for the one color assay.

*Method 3, Antibody Competition:* To prepare for labeling with fluorescein the antibodies were dialyzed or resuspended at a concentration of 1 mg/ml in PBS (pH 8.5). Label ([6-fluorescein-5- (and-6)-carboxamido] hexanoic acid, succinimidyl ester 5(6)-SFX] mixed isomers from Molecular Probes (Eugene, OR, Cat. No. F2181) was added to the protein at a molar ratio 9.5:1 (label: protein) from a label stock of 5mg/ml in DMSO. The mixture was incubated at 4° C overnight in the dark. The labeled antibody was separated from the free label by dialysis in PBS. The FITC/ antibody ratios obtained ranged from 3 to 8. For each competition experiment, a binding reaction was assembled that contained a 50 fold excess (10-50 µg/ml) of unlabeled competitor antibody,  $3.5 \times 10^5$  biotin beads coated with avidin fusion protein in BPBS. The FITC-labeled antibody (1 µg/ml) was added after a 30 min preincubation. The process followed the one color method from this point forward.

Each of the four tested antibodies binds to the IGF-1R L2 domain, as shown in Table 8. However, the precise amino acid contacts of each antibody in the IGF-1R L2 domain may differ.

Table 8

Antibody	L1 <sup>1</sup>	CR <sup>1</sup>	L2 <sup>1</sup>	FnIII-1 <sup>1</sup>	ECD <sup>1,2</sup>
TQ11C	No	No	Yes	No	Yes
TQ25	No	No	Yes	No	Yes
TQ58	Yes	No	Yes	No	Yes
TQ59	No	No	Yes	No	Yes

<sup>1</sup> Epitope mapping was performed with avidin-IGF-1R fusion proteins containing the indicated human IGF-1R regions.

<sup>2</sup> The ECD fusion contains L1+CR+L2+FnIII-1+FnIII-2+ID+FnIII-3.

#### EXAMPLE 13: Antibody Binding to Cell-Surface IGF-1R

This example provides a method for detecting the binding of an anti-IGF-1R antibody to cell-surface expressed IGF-1R.

The ability of antibodies TQ11C, TQ25, TQ58, and TQ59 to bind to human IGF-1R displayed on the cell surface was evaluated using Balb/C 3T3 fibroblasts and MCF-7 human breast cancer cells engineered to overexpress the human IGF-1R receptor at a level of  $\sim 3\text{-}4 \times 10^5$  molecules per cell. A Balb/C 3T3 cell line that stably overexpresses the human IGF-1R ( $\sim 3 \times 10^5$  receptors per cell) was derived using with a retroviral vector essentially as described by Pietrzakowski *et al.*, 1992, Cell Growth Differentiation 3:199-205. MCF-7 breast cancer cells that overproduce huIGF-1R were transfected with a pcDNA3.1 expression vector (Invitrogen Corp.). Zeocin resistant cells that express a high level of hu IGF-1R ( $\sim 4 \times$

$10^5$  receptors per cell) were expanded after selection by FACS using anti-IGF-1R monoclonal antibody  $\alpha$ IR3 and an PE-labeled goat anti murine IgG antibody (Caltag Laboratories, Burlingame, CA). The process of selection and expansion was repeated four times.

IGF-1R Receptor antibody staining and receptor expression was monitored by FACS as follows:

5 the cells were released from T175 flasks (Corning) by washing 2 times with excess PBS (Ca/Mg free) followed by treatment with 5 ml of Cell Dissociation Buffer (Sigma) for 10 min at room temperature. The cells were collected by centrifugation and washed two times by resuspending them in PBS and centrifugation. For primary antibody staining, 1  $\mu$ g of antibody was added to  $10^6$  cells resuspended in 100  $\mu$ l PBS plus 0.5% BSA (BPBS) and the cells were incubated at 4°C for 1.5 hr. The cells were collected by

10 centrifugation and washed twice with BPBS to remove unbound primary antibody. The cells were resuspended in 100  $\mu$ l of BPBS and incubated with 1  $\mu$ g of FITC-labeled goat anti-human F(ab')<sub>2</sub> (Southern Biotechnology Associates, Inc., Birmingham, AL) at 4°C for 30 minutes. After washing to remove unbound FITC secondary antibody, the cells were resuspended in 1 ml of PBS+ 0.5% BSA and FITC cell fluorescence was detected with a FACSCAN (Beckton Dickson Bioscience, Franklin Lakes, NJ).

15 The fluorescence levels were converted to absolute receptor levels using Quantum microbead (Bangs Laboratories, Inc., Fishers, IN) with predetermined IgG1 binding capacity to generate a standard curve. Data reduction was performed with QuickCal v2.1 software (Verity Software House, Topsham, ME) provided by the manufacturer.

The peak fluorescent intensity of anti-IGF-1R antibody labeling of the IGF-1R overexpressors was

20 increased 10-20 fold relative to parental Balb/C 3T3 and MCF-7 cells for each of the tested antibodies. This is the result predicted for an antibody that specifically binds IGF-1R. Background fluorescence of cells treated with no antibodies or FITC-labeled secondary alone were insignificant.

#### EXAMPLE 14: Inhibition of IGF-1R

25 This example presents methods of detecting inhibition of IGF-1R by anti-IGF-1R antibodies.

##### 32D hu IGF-1R+IRS-1 Cell Inhibition

Murine 32D cells that coexpress the human IGF-1R receptor (20K per cell) and human IRS-1 have proven to be a effective system to examine the molecular components IGF-1R signaling Valentinis *et al.*,

30 1999, J Biol Chem 274:12423-30. Normal 32D cells express relatively low levels of the murine orthologs of these two gene products. 32D cell normally required IL3 for growth and survival. IGF-1 or IGF-2 can replace IL3 in 32D huIGF-1R+IRS-1 cells as shown in Figure 16, panel A. The EC<sub>50</sub> to the IGF-1 dose response curve was about 0.5 nM, whereas the IGF-2 EC<sub>50</sub> (2.8 nM) is about six fold higher reflecting weaker affinity of IGF-2 for IGF-1R. To assess the ability of the antibodies TQ11C, TQ25, TQ58, and

35 TQ59 to block IGF-1 or IGF-2 stimulation, 96-well microtitre plates were seeded with 30,000 32D hu IGF-1R+IRS-1 cells per well in a volume of 200  $\mu$ l of RPMI (Gibco/BRL) containing 5% fetal bovine serum (Gibco/BRL) and 1x penicillin, streptomycin, glutamine (Gibco/BRL) and increasing concentrations of antibody ( $10^{-12}$ M to  $10^{-6}$ M) or no antibody. IGF-1 (2 nM), IGF-2 (8 nM) or nothing was added after 1 hr preincubation with antibody. <sup>3</sup>H-thymidine (1  $\mu$ Ci per well) was added at 27 hr post-antibody addition.

40 The cells were harvested 21 hr later, and incorporation of <sup>3</sup>H- thymidine into DNA was determined for each

sample. The assays were performed in triplicate. An anti-CD20 antibody was used as a negative control. Each of antibodies TQ11C, TQ25, TQ58, and TQ59 was able to completely block the IGF-1 and IGF-2 mediated stimulation of the 32D cells. The reduction of background proliferation in the absence of added IGF-1 and IGF-2 is due to the inhibition of serum IGF-1 and IGF-2. The binding data were analyzed using GraphPad PRIZM™ software. The data are shown in Figure 16.

#### Balb/C 3T3 hu IGF-1R Cell Inhibition

IGF-1 greatly stimulates the incorporation of <sup>3</sup>H-thymidine by serum-starved cultures of mouse embryonic fibroblasts (Balb/C 3T3 or NIH 3T3) that overexpress IGF-1R (~1 x 10<sup>6</sup> IGF1R per cell). Kato *et al.*, 1993, J Biol Chem 268:2655-61; Pietrzkowski *et al.*, 1992, Cell Growth Differentiation 3:199-205. This phenomenon is recapitulated with both IGF-1 and IGF-2 in a Balb/C 3T3 cell line hu IGF-1R overexpressor. Both growth factors stimulated <sup>3</sup>H-thymidine incorporation by about 20-fold. The EC<sub>50</sub> of the IGF-1 dose response curve was about 0.7 nM, whereas the IGF-2 EC<sub>50</sub> (4.4 nM) is sevenfold higher, indicating a weaker affinity of IGF-2 for IGF-1R. To assess the ability of a given antibody to block IGF-1 or IGF-2 stimulation, 96-well microtitre plates were seeded with 10,000 cells per well in a volume of 200 µl of DMEM (Gibco/BRL) containing 10% calf serum (Gibco/BRL) and 1x penicillin, streptomycin, glutamine (Gibco/BRL). After overnight incubation when the cells were about 80% confluent the growth medium was replaced with 100 µl DMEM containing 0.1% BSA after washing once with 200 µl PBS. Antibodies at increasing concentrations (10<sup>-12</sup> M to 10<sup>-6</sup> M), or no antibody, were added at 24 hr post-serum starvation. IGF-1 (2 nM), IGF-2 (8 nM) and <sup>3</sup>H-thymidine (1 µCi per well) were added after a 1 hr preincubation with antibody. The cells were harvested 24 hr later, and incorporation of <sup>3</sup>H- thymidine into DNA was determined for each sample. The assays were performed in triplicate. Each tested antibody was able to completely block the IGF-1 and IGF-2 mediated stimulation of Balb/C 3T3 cells, as shown in Figure 17. An anti-CD20 antibody was used as a negative control ("CD20" in Figure 17).

Each reference cited herein is incorporated by reference in its entirety for all that it teaches and for all purposes.

What is claimed is:

1. An isolated antigen binding protein comprising either:

a. a light chain CDR3 comprising a sequence selected from the group consisting of:

i. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L52 as shown in Figure 6;

ii. M X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> X<sub>4</sub> X<sub>5</sub> P X<sub>6</sub> X<sub>7</sub>;

iii. Q Q X<sub>8</sub> X<sub>9</sub> X<sub>10</sub> X<sub>11</sub> P X<sub>12</sub> T; and

iv. Q S Y X<sub>13</sub> X<sub>14</sub> X<sub>15</sub> N X<sub>16</sub> X<sub>17</sub> X<sub>18</sub>;

b. a heavy chain CDR3 comprising a sequence selected from the group consisting of:

i. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the heavy chain CDR3 sequences of H1-H52 as shown in Figure 9;

ii. X<sub>19</sub> X<sub>20</sub> X<sub>21</sub> X<sub>22</sub> X<sub>23</sub> X<sub>24</sub> X<sub>25</sub> X<sub>26</sub> X<sub>27</sub> F D I;

iii. X<sub>28</sub> X<sub>29</sub> X<sub>30</sub> X<sub>31</sub> X<sub>32</sub> X<sub>33</sub> X<sub>34</sub> X<sub>35</sub> X<sub>36</sub> X<sub>37</sub> X<sub>38</sub> M D V;

iv. D S S X<sub>39</sub>; or

c. the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b);

wherein

X<sub>1</sub> is a glutamine residue or a glutamate residue,

X<sub>2</sub> is an alanine residue, a glycine residue, a threonine residue, or a serine residue,

X<sub>3</sub> is a leucine residue, a phenylalanine residue, or a threonine residue,

X<sub>4</sub> is glutamine residue, a glutamate residue, or a histidine residue,

X<sub>5</sub> is a threonine residue, a methionine residue, a tryptophan residue, or a valine residue,

X<sub>6</sub> is a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue,

X<sub>7</sub> is threonine residue, an alanine residue, or a serine residue,

X<sub>8</sub> is an arginine residue, a serine residue, a leucine residue, or an alanine residue,

X<sub>9</sub> is an asparagine residue, a serine residue, or a histidine residue,

X<sub>10</sub> is an asparagine residue or a serine residue,

X<sub>11</sub> is a tryptophan residue, a valine residue, a tyrosine residue, a proline residue, or a phenylalanine residue,

X<sub>12</sub> is a leucine residue, a tyrosine residue, or an isoleucine residue,

X<sub>13</sub> is an aspartate residue or a glutamine residue,

X<sub>14</sub> is a serine residue or a proline residue,

X<sub>15</sub> is a serine residue, a tyrosine residue, an aspartate residue, or an alanine residue,

X<sub>16</sub> is a glutamine residue, an arginine residue, a valine residue, or a tryptophan residue,

X<sub>17</sub> is an arginine residue, a valine residue, an isoleucine residue, or no residue,

X<sub>18</sub> is a valine residue or no residue,

X<sub>19</sub> is a glutamate residue or no residue,

X<sub>20</sub> is a tyrosine residue, a glycine residue, a serine residue, or no residue,

X<sub>21</sub> is a serine residue, an asparagine residue, a tryptophan residue, a glutamate residue, an aspartate residue, or no residue,

X<sub>22</sub> is a serine residue, an aspartate residue, a tryptophan residue, an alanine residue, an arginine residue, a threonine residue, a glutamine residue, a leucine residue, a glutamate residue, or no residue,

X<sub>23</sub> is a serine residue, a glycine residue, an asparagine residue, a threonine residue, a tryptophan residue, a valine residue, an alanine residue, or an isoleucine residue,

X<sub>24</sub> is an arginine residue, a glutamine residue, a tyrosine residue, a valine residue, an alanine residue, a glycine residue, a serine residue, a phenylalanine residue, or a tryptophan residue,

X<sub>25</sub> is an asparagine residue, a leucine residue, an aspartate residue, a threonine residue, a tryptophan residue, a tyrosine residue, a valine residue, an alanine residue, or a histidine residue,

X<sub>26</sub> is an aspartate residue, a serine residue, an asparagine residue, or a glutamine residue,

X<sub>27</sub> is an alanine residue or a proline residue,

X<sub>28</sub> is an alanine residue or no residue,

X<sub>29</sub> is a glutamate residue, a tyrosine residue, a glycine residue, or no residue,

X<sub>30</sub> is an arginine residue, a serine residue, or no residue,

X<sub>31</sub> is a glycine residue, an aspartate residue, a valine residue, a serine residue, or no residue,

X<sub>32</sub> is a serine residue, an aspartate residue, a glycine residue, or no residue,

X<sub>33</sub> is a phenylalanine residue, an aspartate residue, a tyrosine residue, a glycine residue, a serine residue, a histidine residue, a tryptophan residue, or no residue,

X<sub>34</sub> is a tryptophan residue, an aspartate residue, a tyrosine residue, a serine residue, or no residue,

X<sub>35</sub> is an aspartate residue, a glutamate residue, an arginine residue, a serine residue, a glycine residue, a tyrosine residue, or a tryptophan residue,

X<sub>36</sub> is a tyrosine residue, a lysine residue, an isoleucine residue, a leucine residue or a phenylalanine residue,

X<sub>37</sub> is a tyrosine residue, a serine residue, a phenylalanine residue, an aspartate residue, or a glycine residue,

X<sub>38</sub> is a glycine residue, an asparagine residue, or a tyrosine residue,

X<sub>39</sub> is a valine residue, a glycine residue, or a serine residue,

and said antigen binding protein binds specifically to human IGF-1R.

2. The isolated antigen binding protein of Claim 1, comprising an amino acid sequence selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;

- c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

3. The isolated antigen binding protein of Claim 2, comprising an amino acid sequence selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of L1-L52 as shown in Figure 5;
- c. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

4. The isolated antigen binding protein of Claim 3, comprising an amino acid sequence selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR2 sequence of L1-L52 as shown in Figure 5;
- c. a light chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

5. The isolated antigen binding protein of Claim 4, comprising an amino acid sequence selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR3 sequence of L1-L52 as shown in Figure 6;
- c. a heavy chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- d. a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9.

6. The isolated antigen binding protein of Claim 5, comprising an amino acid sequence selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a heavy chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- c. a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9.

7. The isolated antigen binding protein of Claim 6, comprising an amino acid sequence selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of L1-L52 as shown in Figure 4; and
- b. a heavy chain CDR2 sequence of H1-H52 as shown in Figure 8.

8. The isolated antigen binding protein of Claim 7, comprising a CDR1 sequence of L1-L52 as shown in Figure 4.

9. The isolated antigen binding protein of Claim 1, comprising a sequence selected from the group consisting of:

- a. a light chain CDR1 sequence selected from the group consisting of:
  - i. RSSQSLLHSNGYNYLD;
  - ii. RASQ(G/S)(I/V)(G/S)X(Y/F)L(A/N); and
  - iii. RSSQS(L/I)XXXXXX;
- b. a light chain CDR2 sequence selected from the group consisting of:
  - i. LGSNRAS;
  - ii. AASTLQS; and
  - iii. EDNXRPS;
- c. a heavy chain CDR1 sequence selected from the group consisting of:
  - i. SSNWWS;
  - ii. XYYWS; and
  - iii. SYAM(S/H); and
- d. a heavy chain CDR2 sequence selected from the group consisting of:

- i. (E/I)(I/V)(Y/N)(H/Y)SGST(N/Y)YNPSLKS; and
- ii. XIS(G/S)SG(G/S)STYYADSVKG;

wherein amino acid residue symbols enclosed in parentheses identify alternative residues for the same position in a sequence, each X is independently any amino acid residue, and each Z is independently a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue.

10. The isolated antigen binding protein of Claim 1, comprising a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

11. The isolated antigen binding protein of Claim 10, comprising a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9.

12. The isolated antigen binding protein of Claim 11, comprising a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9.

13. The isolated antigen binding protein of Claim 1, comprising two amino acid sequences selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;
- c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

14. The isolated antigen binding protein of Claim 13, comprising three amino acid sequences selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;



- c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

15. The isolated antigen binding protein of Claim 14, comprising four amino acid sequences selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;
- c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

16. The isolated antigen binding protein of Claim 15, comprising five amino acid sequences selected from the group consisting of:

- a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;
- c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

17. The isolated antigen binding protein of Claim 16, comprising:

- a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;
- b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;
- c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;
- d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;
- e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and
- f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

18. The isolated antigen binding protein of Claim 1, comprising either:

- a. a light chain variable domain comprising:
  - i. a light chain CDR1 sequence shown in Figure 4;
  - ii. a light chain CDR2 sequence shown in Figure 5; and
  - iii. a light chain CDR3 sequence shown in Figure 6;
- b. a heavy chain variable domain comprising:
  - i. a heavy chain CDR1 sequence shown in Figure 7;
  - ii. a heavy chain CDR2 sequence shown in Figure 8; and
  - iii. a heavy chain CDR3 sequence shown in Figure 9; or
- c. the light chain variable domain of (a) and the heavy chain variable domain of (b).

19. The isolated antigen binding protein of Claim 18, comprising either:

- a. light chain CDR1, CDR2, and CDR3 sequences that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same light chain variable domain sequence selected from the group consisting of L1-L52;
- b. heavy chain CDR1, CDR2, and CDR3 sequences that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same heavy chain variable domain sequence selected from the group consisting of H1-H52; or
- c. the light chain CDR1, CDR2, and CDR3 sequences of (a) and the heavy chain CDR1, CDR2, and CDR3 sequences of (b).

20. An isolated antigen binding protein comprising either:

- a. a light chain variable domain sequence selected from the group consisting of:
  - i. a sequence of amino acids at least 80% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;
  - ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2;

- iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and
  - iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1;
    - b. a heavy chain variable domain sequence selected from the group consisting of:
      - i. a sequence of amino acids at least 80% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;
      - ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;
      - iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; and
      - iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or
    - c. the light chain variable domain of (a) and the heavy chain variable domain of (b);
- wherein said antigen binding protein binds to human IGF-1R.

21. The isolated antigen binding protein of Claim 20, comprising either:

- a. a light chain variable domain sequence selected from the group consisting of:
  - i. a sequence of amino acids at least 85% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;
  - ii. a sequence of amino acids comprising at least 25 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2;
  - iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and
  - iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1;
- b. a heavy chain variable domain sequence selected from the group consisting of:
  - i. a sequence of amino acids at least 85% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;
  - ii. a sequence of amino acids comprising at least 25 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;
  - iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; and

iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

22. The isolated antigen binding protein of Claim 21, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 90% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 35 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 90% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 35 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

23. The isolated antigen binding protein of Claim 22, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 95% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 95% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 95% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 95% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

24. The isolated antigen binding protein of Claim 23, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 97% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 97% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

25. The isolated antigen binding protein of Claim 24, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 99% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 99% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 99% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 99% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c. the light chain variable domain of (a) and the heavy chain variable domain of (b).

26. The isolated antigen binding protein of Claim 25 comprising either:

a. a light chain variable domain sequence selected from the group consisting of L1-L52 as shown in Figure 2;

b. a heavy chain variable domain sequence selected from the group consisting of H1-H52 as shown in Figure 3; or

c. the light chain variable domain of (a) and the heavy chain variable domain of (b).

27. The isolated antigen binding protein of Claim 26 comprising a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52.

28. The isolated antigen binding protein of Claim 27 further comprising:

a. the kappa light chain constant sequence of Figure 13,

b. the IgG1 heavy chain constant sequence of Figure 13, or

c. the kappa light chain constant sequence of Figure 13 and the IgG1 heavy chain constant sequence of Figure 13.

29. The isolated antigen binding protein of Claim 1 or Claim 20, that, when bound to IGF-1R:

a. inhibits IGF-1R;

b. activates IGF-1R;

c. cross-competes with a reference antibody for binding to IGF-1R;

d. binds to the same epitope of IGF-1R as said reference antibody;

e. binds to IGF-1R with substantially the same  $K_d$  as said reference antibody; or

f. binds to IGF-1R with substantially the same off rate as said reference antibody;

wherein said reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52.

30. The isolated antigen binding protein of Claim 1 or Claim 20, that, when bound to a human IGF-1R, inhibits binding of IGF-1 and/or IGF-2 to said human IGF-1R.
31. The isolated antigen binding protein of Claim 1 or Claim 20, that inhibits the growth of a cancer cell by greater than about 80% in the presence of a growth stimulant selected from the group consisting of serum, IGF-1, and IGF-2.
32. The isolated antigen binding protein of Claim 31, wherein said cancer cell is an MCF-7 human breast cancer cell.
33. The isolated antigen binding protein of Claim 1 or Claim 20, that binds to human IGF-1R with a selectivity that is at least fifty times greater than its selectivity for human insulin receptor.
34. The isolated antigen binding protein of Claim 1 or Claim 20, that inhibits tumor growth *in vivo*.
35. The isolated antigen binding protein of Claim 1 or Claim 20, that inhibits IGF-1R mediated tyrosine phosphorylation.
36. The isolated antigen binding protein of Claim 1 or Claim 20, that specifically binds to the IGF-1R of a non-human primate, a cynomolgous monkey, a chimpanzee, a non-primate mammal, a rodent, a mouse, a rat, a hamster, a guinea pig, a cat, or a dog.
37. The isolated antigen binding protein of Claim 1 or Claim 20 wherein said antigen binding protein comprises:
- a. a human antibody;
  - b. a humanized antibody;
  - c. a chimeric antibody;
  - d. a monoclonal antibody;
  - e. a polyclonal antibody;
  - f. a recombinant antibody;
  - g. an antigen-binding antibody fragment;
  - h. a single chain antibody;
  - i. a diabody;
  - j. a triabody;
  - k. a tetrabody;
  - l. a Fab fragment;
  - m. a F(ab')<sub>2</sub> fragment;
  - n. a domain antibody;
  - o. an IgD antibody;

- p. an IgE antibody;
  - q. an IgM antibody;
  - r. an IgG1 antibody;
  - s. an IgG2 antibody;
  - t. an IgG3 antibody;
  - u. an IgG4 antibody; or
  - v. an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.
38. An isolated polynucleotide comprising a sequence that encodes the light chain, the heavy chain, or both of said antigen binding protein of Claim 1 or Claim 20.
39. The isolated polynucleotide of Claim 38, wherein said polynucleotide comprises a light chain variable domain nucleic acid sequence of Figure 1 and/or a heavy chain variable domain nucleic acid sequence of Figure 1.
40. A plasmid comprising said isolated polynucleotide of Claim 38.
41. The plasmid of Claim 40, wherein said plasmid is an expression vector.
42. An isolated cell comprising said polynucleotide of Claim 38.
43. The isolated cell of Claim 42, wherein a chromosome of said cell comprises said polynucleotide.
44. The isolated cell of Claim 42, wherein said cell is a hybridoma.
45. The isolated cell of Claim 42, wherein an expression vector comprises said polynucleotide.
46. The isolated cell of Claim 42, wherein said cell is a CHO cell.
47. A method of making an antigen binding protein that binds human IGF-1R, comprising incubating said isolated cell of Claim 42 under conditions that allow it to express said antigen binding protein.
48. A pharmaceutical composition comprising the antigen binding protein of Claim 1 or Claim 20.
49. A method of treating a condition in a subject comprising administering to said subject said pharmaceutical composition of Claim 48, wherein said condition is treatable by reducing the activity of IGF-1R in said subject.
50. The method of Claim 49 wherein said subject is a human being.



51. The method of Claim 49 wherein said condition is multiple myeloma, a liquid tumor, liver cancer, a thymus disorder, a T-cell mediated autoimmune disease, an endocrinological disorder, ischemia, or a neurodegenerative disorder.

52. The method of claim 51 wherein said liquid tumor is selected from the group consisting of acute lymphocytic leukemia (ALL) and chronic myelogenous leukemia (CML); wherein said liver cancer is selected from the group consisting of hepatoma, hepatocellular carcinoma, cholangiocarcinoma, angiosarcomas, hemangiosarcomas, hepatoblastoma; wherein said thymus disorder is selected from the group consisting of thymoma and thyroiditis, wherein said T-cell mediated autoimmune disease is selected from the group consisting of Multiple Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE), Grave's Disease, Hashimoto's Thyroiditis, Myasthenia Gravis, Auto-Immune Thyroiditis, Bechet's Disease, wherein said endocrinological disorder is selected from the group consisting of Type II Diabetes, hyperthyroidism, hypothyroidism, thyroiditis, hyperadrenocorticism, and hypoadrenocorticism; wherein said ischemia is post cardiac infarct ischemia, or wherein said neurodegenerative disorder is Alzheimer's Disease.

53. The method of Claim 49 wherein said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an overdose of acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy.

54. The method of Claim 49 further comprising administering to said subject a second treatment.

55. The method of Claim 54 wherein said second treatment is administered to said subject before and/or simultaneously with and/or after said pharmaceutical composition is administered to said subject.

56. The method of Claim 54 wherein said second treatment comprises radiation treatment, surgery, or a second pharmaceutical composition.

57. The method of Claim 56 wherein said second pharmaceutical composition comprises an agent selected from the group consisting of a corticosteroid, an anti-emetic, ondansetron hydrochloride, granisetron hydrochloride, metoclopramide, domperidone, haloperidol, cyclizine, lorazepam, prochlorperazine, dexamethasone, levomepromazine, tropisetron, a cancer vaccine, a GM-CSF inhibiting agent, a GM-CSF

DNA vaccine, a cell-based vaccine, a dendritic cell vaccine, a recombinant viral vaccine, a heat shock protein (HSP) vaccine, an allogeneic tumor vaccine, an autologous tumor vaccine, an analgesic, ibuprofen, naproxen, choline magnesium trisalicylate, an oxycodone hydrochloride, an anti-angiogenic agent, an anti-vascular agent, bevacizumab, an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fragment, an anti-TWEAK antibody, an anti-TWEAK receptor antibody, a soluble TWEAK receptor fragment, AMG 706, AMG 386, an anti-proliferative agent, a farnesyl protein transferase inhibitor, an  $\alpha v\beta 3$  inhibitor, an  $\alpha v\beta 5$  inhibitor, a p53 inhibitor, a Kit receptor inhibitor, a ret receptor inhibitor, a PDGFR inhibitor, a growth hormone secretion inhibitor, an angiopoietin inhibitor, a tumor infiltrating macrophage-inhibiting agent, a c-fms inhibiting agent, an anti-c-fms antibody, an CSF-1 inhibiting agent, an anti-CSF-1 antibody, a soluble c-fms fragment, pegvisomant, gemcitabine, panitumumab, irinotecan, and SN-38.

58. The method of Claim 54 further comprising administering to said subject a third treatment.

59. The method of Claim 58, wherein said condition is a cancer, said second treatment comprises administering panitumumab, and said third treatment comprises administering gemcitabine.

60. The method of Claim 49 wherein said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an overdose of acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy.

61. A method of increasing the longevity of a subject comprising administering to said subject said pharmaceutical composition of Claim 48.

62. A method of decreasing IGF-1R activity in a subject in need thereof comprising administering to said subject said pharmaceutical composition of Claim 48.

63. A method of decreasing IGF-1R signaling in a subject in need thereof comprising administering to said subject said pharmaceutical composition of Claim 48.

64. A method of inhibiting the binding of IGF-1 and/or IGF-2 to IGF-1R in a subject in need thereof comprising administering to said subject said pharmaceutical composition of Claim 48.

Figure 1

**L1 (SEQ ID NO:1)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAGTGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTTCAG  
 TGGCAGTGGG TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCGATC ACCTTCGGCC AAGGGACACG ACTGGAGATT AAA

**L2 (SEQ ID NO:3)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTTCAG  
 TGGCAGTGGG TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCGATC ACCTTCGGCC AAGGGACACG ACTGGAGATT AAA

**L3 (SEQ ID NO:5)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTTCAG  
 TGGCAGTGGG TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCACTC ACTTTCGGCG GCGGGACCAA GGTGGAGATC AAA

**L4 (SEQ ID NO:7)**

GA AATTGTGATG ACGCAGTCTC CACTCTCCCT GCCGTCACCC CCTGGAGAGC CGGCCTCCAT  
 CTCCTGCAGG TCTAGTCAGA GCCTCCTGCA TAGTAATGGA TACAACTATT TGGATTGGTA CCTGCAGAAG  
 CCAGGGCAGT CTCCACAGCT CCTGATCTAT TTGGGTTCTA ATCGGGCCTC CGGGTCCCTGA CACAGGTTCA  
 GTGGCAGTGG ATCAGGCACA GATTTTACAC TGAATAATCAG CAGAGTGGAG GCTGAGGATG TTGGGGTTTA  
 TTACTGCATG CAAGCTCTAC AAACCTCCTCA CACTTTCGGC GGAGGGACCA AGGTGGAGAT CAAA

**L5 (SEQ ID NO:9)**

GAAA TTGTGCTGAC TCAGTCTCCA CTCTCCCTGC CCGTCACCCC TGGAGAGCCG GCCTCCATCT  
 CCTGCAGGTC TAGTCAGAGC CTCCTGCATA GTAATGGATA CAACTATTTG GATTGGTACC TGCAGAAGCC  
 AGGGCAGTCT CCACAGCTCC TGATCTATTT CGGGCCTCCG GGGTCCCTGA CAGGTTTCAGT  
 GGCAGTGGAT CAGGCACAGA TTTTACACTG AAAATCAGCA GAGTGGAGGC TGAGGATGTT GGGGTTTATT  
 ACTGCATGCA AGCTCTACAA ACCCCTCTCA CTTTCGGCCC TGGGACCAA GTGGATATCA AA

**L6 (SEQ ID NO:11)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG GCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTTCAG  
 TGGCAGTGGG TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCGCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

**L7 (SEQ ID NO:13)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTTCAG  
 TGGCAGTGGG TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCTCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

**L8 (SEQ ID NO:15)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC  
 AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC  
 AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG  
 TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAAG ATGTTGGGGT TTATTACTGT  
 ATGCAAGCTC TACAAACCCC CCTCACTTTC GGCGGAGGGA CCAAGGTGGA GATCAA

**L9 (SEQ ID NO:17)**

GATG TTGTGATGAC TCAGTCTCCA CTCTCCCTGC CCGTCACCCC TGGAGAGCCG GCCTCCATCT  
 CCTGCAGGTC TAGTCAGAGC CTCCTGCATA GTAATGGATA CAACTATTTG GATTGGTACC TGCAGAAGCC  
 AGGGCAGTCT CCACAGCTCC TGATCTATTT GGGTTCTAAT CGGGCCTCCG GGGTCCCTGA CAGGTTTCAGT  
 GGCAGTGGAT CAGGCACAGA TTTTACACTG AAAATCAGCA GAGTGGAGGC TGAGGATGTT GGGGTTTATT  
 ACTGCATGCA AGCTCTACAA ACTCCGTTCA CCTTCGGCCA AGGGACACGA CTGGAGATTA AA

**L10 (SEQ ID NO:19)**

GATGTTGTGA	TGACTCAGTC	TCCACTCTCC	CTGCCCCGTCA	CCCCTGGAGA	GCCGGCCTCC	ATCTCCTGCA
GGTCTAGTCA	GAGCCTCCTG	CATAGTAATG	GATACAACATA	TTTGGATTGG	TACCTGCAGA	AGCCAGGGCA
GTC'TCCACAG	CTCCTGATCT	ATTTGGGTTC	TAATCGGGCC	TCCGGGGTCC	CTGACAGGTT	CAGTGGCAGT
GGATCAGGCA	CAGATTTTAC	ACTGAAAATC	AGCAGAGTGG	AGGCTGAGGA	TGTTGGGGTT	TATTACTGCA
TGCAAGCTCT	ACAAACTCCT	CTGGCGTTCC	GCCAAGGGAC	CAAGGTGGAA	ATCAAA	

**L11 (SEQ ID NO:21)**

GAAATTGT	GCTGACTCAG	TCTCCACTCT	CCCTGCCCCGT	CACCCCTGGA	GAGCCGGCCT	CCATCTCCTG
CAGGTCTAGT	CAGAGCCTCC	TGCATAGTAA	TGGATACAAC	TATTTGAATT	GGTACCTGCA	GAAGCCAGGG
CAGTCTCCAC	AGCTCCTGAT	CTATTTGGGT	TCTAATCGGG	CCTCCGGGGT	CCCTGACAGG	TTCAGTGCCA
GTGGATCAGG	CACAGATTTT	ACACTGAAAA	TCAGCAGAGT	GGAGGCTGAG	GATGTTGGGG	TTTATTACTG
CATGCAAGCT	CTACAAACTC	CTATCACCTT	CGGCCAAGGG	ACACGACTGG	AGATTAAA	

**L12 (SEQ ID NO:23)**

AATT	TTATGCTGAC	TCAGCCCCAC	TCTGTGTCGG	AGTCTCCGGG	GAAGACGGTA	ACCATCTCCT
GCACCCGCAG	CAGTGGCAGC	ATTGCCAGCA	ACTATGTGCA	GTGGTACCAG	CAGCGCCCCG	GCAGTTCCCC
CACCACTGTG	ATCTATGAGG	ATAACCAAAG	ACCCCTCTGGG	GTCCCTGATC	GGTCTCTTGG	CTCCATCGAC
AGCTCCTCCA	ACTCTGCCTC	CCTCACCATC	TCTGGACTGA	AGACTGAGGA	CGAGGCTGAC	TACTACTGTC
AGTCTTATGA	TAGCAGCAAT	CAGAGAGTGT	TCGGCGGAGG	GACCAAGCTG	ACCGTCCTA	

**L13 (SEQ ID NO:25)**

GAT	GTGTGTGATGA	CTCAGTCTCC	ACTCTCCCTG	CCCGTCACCC	CTGGAGAGCC	GGCCTCCATC
TCCTGCAAGGT	CTAGTCAGAG	CCTCCTGTCAT	AGTAATGGAT	ACAACTATTT	GGATTGGTAC	CTGCAGAAGC
CAGGGCAGTC	TCCACAGCTC	CTGATCTATT	TGGGTCTTAA	TCGGGCCTCC	GGGGTCCCTG	ACAGGTTTCAG
TGGCAGTGGA	TCAGGCACAG	ATTTTACACT	GAAAAATCAGC	AGAGTGGAGG	CTGAGGATGT	TGGGGTTTAT
TACTGCATGC	AAGCTCTACA	AACCCCGCTC	ACTTTCCGCG	GAGGGACCAA	GGTGGAGATC	AAA

**L14 (SEQ ID NO:27)**

G	ATGTTGTGAT	GA CT CAGTCT	CCACTCTCCC	TGCCCGTCAC	CCCTGGAGAG	CCGGCCTCCA
TCTCCTGCAG	GTCTAGTCAG	AGCCTCCTGC	ATAGTAATGG	ATACAACTAT	TTGGATTGGT	ACCTGCAGAA
GCCAGGGCAG	TCTCCACAGC	TCCTGATCTA	TTTGGGTTCT	AATCGGGCCT	CCGGGGTCCC	TGACAGGTTT
AGTGGCAGTG	AGATTTTACA	CTGAAAAATCA	GCAGAGTGGA	GGCTGAGGAT	GGTGGGGTTT	
ATTACTGCAT	GCAAGCTCTA	CAAACCTCCT	TTACTTTTCGG	CGGAGGGACC	AAGGTGGAGA	TCAAA

**L15 (SEQ ID NO:29)**

GATGTTGTG	ATGACTCAGT	CTCCACTCTC	CCTGCCCCGTC	ACCCCTGGAG	AGCCGGCCTC	CATCTCCTGC
AGGTCTAGTC	AGAGCCTCCT	GCATAGTAAT	GGATACAAC	ATTTGGATTG	GTACCTGCAA	AAGCCAGGGC
AGTCTCCACA	GCTCCTGATC	TATTTGGGTT	CTTATCGGGC	CTCCGGGGTC	CCTGACAGGT	TCAGTGCCAG
TGGATCAGGC	ACAGATTTTA	CACTGAAAAT	CAGCAGAGTG	GAGGCTGAGG	ATGTTGGGGT	TTATTACTGC
ATGCAAGCTC	TACAAACTCC	GATCACCTTC	GGCCAAGGGA	CACGACTGGA	GATTAAA	

**L16 (SEQ ID NO:31)**

GATGTTGTG	ATGACTCAGT	CTCCACTCTC	CCTGCCCCGTC	ACCCCTGGAG	AGCCGGCCTC	CATCTCCTGC
AGGTCTAGTC	AGAGCCTCCT	GCATAGTAAT	GGATACAAC	ATTTGGATTG	GTACCTGCA	AAGCCAGGGC
AGTCTCCACA	GCTCCTGATC	TATTTGGGTT	CTAATCGGGC	CTCCGGGGTC	CCTGACAGGT	TCAGTGCCAG
TGGATCAGGC	ACAGATTTTA	CACTGAAAAT	CAGCAGGGTG	GAGGCTGAGG	ATGTTGGGGT	TTATTACTGC
ATGCAAGGTA	CACACTGGCC	TCTGACGTTT	GGCCAAGGGA	CCAAGGTGGA	GATCAAA	

**L17 (SEQ ID NO:33)**

GAAATTG	TGATGACGCA	GTCTCCACTC	TCCCTGCCCCG	TCACCCCTGG	AGAGCCGGCC	TCCATCTCCT
GCAGGTCTAG	TCAGAGCCTC	CTGCATAGTA	ATGGATACAA	CTATTTGGAT	TGGTACCTGC	AGAAGCCAGG
GCAGTCTCCA	CAGCTCCTGA	TCTATTTGGG	TTCTAATCGG	GCCTCCGGGG	TCCCTGACAG	GTTCAAGTGG
AGTGGATCAG	GCACAGATTT	TACACTGAAA	ATCAGCAGAG	TGGAGGCTGA	GGATGTTGGG	GTTTATTACT
GCATGCAAGC	TCTACAAACT	CCTCTCACTT	TCGGCGGAGG	GACCAAGGTG	GAGATCAAA	

**L18 (SEQ ID NO:35)**

GAC	ATCCAGTTGA	CCCAGTCTCC	ATCTTCCGTG	TCTGCGTCTG	TCGGAGACAG	AGTCACCATC
ACTTGTGCGG	CGAGTCAGGG	TATTAGCAGG	TGGTTAGCCT	GGTATCAACA	GAAACCAGGG	AAAGCCCCCTA
GACTCCTGAT	CTATGCTGCG	TCCGGTTTAC	AAAGTGGGGT	CCCATCAAGG	TTCAGCGGCA	GTGGATCTGG
GACAGATTTT	ACTCTCACCA	TCAGCAACCT	GCAGCCTGAA	GATTTTGCAA	CTTACTATTG	TCAACAGGCT
AGCAGTTTTC	CAATCACCTT	CGGCCAAGGG	ACACGACTGG	AGACTAAA		

**L19 (SEQ ID NO:37)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTCTCTAA TCGGGCCTCC GGGGTCCCCTG ACAGGTTTCTAG  
 TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGAGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCGTAC ACTTTTGGCC AGGGGACCAA GCTGGAGATC AAA

**L20 (SEQ ID NO:39)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC  
 AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACCT ATTTGGATTG GTACCTGCAG AAGCCAGGGC  
 AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTAACAGGT TCAGTGGCAG  
 TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC  
 ATGCAAGCTC TACAACTCC ATTCACTTTC GGCCCTGGGA CCAAAGTGGG TATCAAA

**L21 (SEQ ID NO:41)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC  
 AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACCT ATTTGGATTG GTACCTGCAG AAGCCAGGGC  
 AGTCTCCACA ACTTCTGATC TATTTGGGTT CTTATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG  
 TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC  
 ATGCAATCTC TAGAAGTTCC GTTCACTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA

**L22 (SEQ ID NO:43)**

TCT TCTGAGCTGA CTCAGGACCC TGCTGTGTCT GTGGCCTTGG GACAGACAGT CAGGATCACA  
 TGCCAAGGAG ACAGCCTCAG AATTTATTAT ACAGGCTGGT ACCAACAGAA GCCAGGACAG GCCCCTGTGC  
 TTGTCTCTTT TGGTAAGAAC AATCGGCCCT CAGGGATCCC AGACCGATTC TCTGGCTCCC ACTCAGGGAA  
 CACAGCTTCC TTGACCATCA CTGGGGCTCA AGCGGAAGAT GAGGCTGACT ATTACTGTAA CTCCCGGGAC  
 ATCACTGGTG TCCATCGATT CGGCGGAGGG ACCAAGCTGA CCGTCTCA

**L23 (SEQ ID NO:45)**

GAA ATTGTGCTGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTCTCTAA TCGGGCCTCC GGGGTCCCCTG ACAGGTTTCTAG  
 TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCTCTC ACTTTCCGGC GAGGGACCAA GGTGGAGATC AAA

**L24 (SEQ ID NO:47)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTCTCTAA TCGGGCCTCC GGGGTCCCCTG ACAGGTTTCTAG  
 TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCTAAC ACTTTCCGGC GAGGGACCAA GGTGGAGATC AAA

**L25 (SEQ ID NO:49)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC  
 AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACCT ATTTGGATTG GTACCTGCAG AAGCCAGGGC  
 AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG  
 TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC  
 ATGCAAGCTC TACAACTCC AATCACTTTC GGCCCTGGGA CCAAAGTGGG TATCAAA

**L26 (SEQ ID NO:51)**

GATGTTGTG ATGACTCAGT TCTCCACTCT CCCTGCCCGT CACCCCTGGA GAGCCGGCCT CCATCTCCTG  
 CAGGTCTAGT CAGAGCCTCC TGCATAGTAA TGGATACACC TATTTGGATT GGTACCTGCA GAAGCCAGGG  
 CAGTCTCCAC AACTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG TTCAGCGGCA  
 GTGGATCAGG CACAGATTTT AACTGAAAA TCAGCAGAGT GGAGCCTGAG GATGTTGGGG TCTATTACTG  
 CATGCAAGCT CTAGAAATGC CCCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA

**L27 (SEQ ID NO:53)**

GAC ATCCAGTTGA CCCAGTCTCC ATCCTTCTCTG TCTGCATCTG TAGGAGACAG AGTCACCATC  
 ACTTGCCGGG CCAGTCAGGG CATTAGCAGT TATTTAGCCT GGTATCAGCA AAAACCAGGG AAAGCCCTTA  
 AGTCTCTGAT CTATGCTGCA TCCACTTTGC AAAGTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG  
 GACAGAATTC ACTCTCACA TCAGCAGCCT GCAGCCTGAA GATTTTGCAA CTTATTACTG TCAACAGCTT  
 AATAGTTACC CCCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA

**L28 (SEQ ID NO:55)**

TC	CTATGTGCTG	ACTCAGCCAC	CCTCAGTGTC	CGTGTCCTCCA	GGACAGACAG	CCAGCATCAC
CTGCTCTGGA	GATAAATTGG	GGGATAAATA	TGTTGGCTGG	TATCAGCAAA	AGGCAGGCCA	AGCCCCCTGTT
TTGGTCATCT	ATCAAGACAA	CAAGCGACCC	TCAGGGATCC	CTGAGCGATT	CTCTGGCTCC	AACTCTGGGA
ACACAGCCAG	TCTGACCATC	AGCGGGACCC	AGGCTATGGA	TGAGGCTGAC	TATTACTGTC	AGGCGTGGGA
CAGCGCACG	GTGTTCCGGC	GAGGGACCAA	GCTGACCGTC	CTA		

**L29 (SEQ ID NO:57)**

GATG	TTGTGATGAC	TCAGTCTCCA	CTCTCCCTGC	CCGTCACCCC	TGGAGAGCCG	GCCTCCATCT
CCTGCAGGTC	TAGTCAGAGC	CTCCTGCATA	GTAATGGATA	CAACTATTTG	GATTGGTACC	TGCAGAAGCC
AGGGCAGTCT	CCACAGCTCC	TGATCTATTT	GGGTTCCTAAT	CGGGCCTCCG	GGGTCCCTGA	CAGGTTTCACT
GGCAGTGGAT	CAGGCACAGA	TTTTACACTG	AAAATCAGCA	GAGTGGAGGC	TGAGGATGTT	GGGGTTTATT
ACTGCATGCA	AGCTCTACAA	ACCCCCCTCA	CTTTCGGCGG	AGGGACCAAG	GTGGAGATCA	AA

**L30 (SEQ ID NO:59)**

GATGTTGTG	ATGACTCAGT	CTCCACTCTC	CCTGCCCGTC	ACCCCTGGAG	AGCCGGCCTC	CATCTCCTGC
AGGTCCTAGTC	AGAGCCTCCT	GCATAGTAAT	GGATACAAC	ATTTGGATTG	GTACCTGCAG	AAGCCAGGGC
AGTCTCCACA	GCTCCTGATC	TATTTGGGTT	CTAATCGGGC	CTCCGGGGTC	CCTGACAGGT	TCAGTGGCAG
TGGATCAGGC	ACAGATTTTA	CACTGAAAAT	CAGCAGAGTG	GAGGCTGAGG	ATGTTGGGGT	TTATTACTGC
ATGGAAGCTC	TACAAACTCC	ATTCACTTTC	GGCCCTGGGA	CCAAGGTGGA	AATCAAA	

**L31 (SEQ ID NO:61)**

GACATC	CAGTTGACCC	AGTCTCCATC	CTCCCTGTCT	GCGTCTGTGG	GAGACAGAGT	CACCATCACT
TGCCCCGTC	GTCAAGGCAT	TGGTTACTTC	TTAAATTTGGT	ATCAGCAGGA	ACCAGGGAAA	GCCCCAAAGA
TCCTGATCTC	TGCTGCATCC	ACTTTGCAAA	GTGGGGTCCC	ATCAAGGTTT	AGTGGCAGTG	GATCTGGGAC
AGATTTTACA	CTCTCCATCA	ACAATCTGCA	ACCCGCAGAT	TTTGGCGACAT	ACTACTGTCA	ACAGAGTCAC
AGTCCCCCGT	ACACTTTTCGG	CCAGGGGACC	AAGGTGGAGA	TCAA		

**L32 (SEQ ID NO:63)**

GAT	GTTGTGATGA	CTCAGTCTCC	ACTCTCCCTG	CCCGTCACCC	CTGGAGAGCC	GGCCTCCATC
TCCTGCAGGT	CTAGTCAGAG	CCTCCTGCAT	AGTAATGGAT	ACAACTATTT	GGATTGGTAC	CTGCAGAAGC
CAGGGCAGTC	TCCACAGCTC	CTGATCTATT	TGGGTTCTAA	TCGGGCCTCC	GGGGTCCCTG	ACAGGGTTTCA
TGGCAGTGGG	TCCAGGCACAG	ATTTTACACT	GAAAATCAGC	AGAGTGGAGG	CTGAGGATGT	TGGGGTTTAT
TACTGCATGC	AAGCTCTACA	AACTCCGCTC	ACTTTCGGCG	GAGGGACCAA	GGTGGAGATC	AAA

**L33 (SEQ ID NO:65)**

GAAATTGTG	CTGACTCAGT	CTCCACTCTC	CCTGCCCGTC	ACCCCTGGAG	AGCCGGCCTC	CATCTCCTGC
AGGTCCTAGTC	AGAGCCTCCT	GCATAGTAAT	GGATACAAC	ATTTGGATTG	GTACCTGCAG	AAGCCAGGGC
AGTCTCCACA	GCTCCTGATG	TATTTGGTTC	CTAATCGGGC	CTCCGGGGTC	CCTGAGAGGT	TCAGTGGCAG
TGGATCAGGC	ACAGATTTTA	CACTGAAAAT	CAGCAGAGTG	GAGGCTGAGG	ATGTTGGGGT	TTATTACTGC
ATGCAAACTC	TACAAACTCC	TCTCAGTTTT	GGCCAGGGGA	CCAAGCTGGA	GATCAAA	

**L34 (SEQ ID NO:67)**

GATGTTGTG	ATGACTCAGT	CTCCACTCTC	CCTGCCCGTC	ACCCCTGGAG	AGCCGGCCTC	CATCTCCTGC
AGGTCCTAGTC	AGAGCCTCCT	GCATAGTAAT	GGATACAAC	ATTTGGATTG	GTACCTGCAG	AAGCCAGGGC
AGTCTCCACA	GCTCCTGATC	TATTTGGGTT	CTAATCGGGC	CTCCGGGGTC	CCTGACAGGT	TCAGTGGCAG
TGGATCAGGC	ACAGATTTTA	CACTGAAAAT	CAGCAGAGTG	GAGGCTGAGG	ATGTTGGGGT	TTATTACTGC
ATGCAAGCTC	TACAAACTCC	GCTCACTTTC	GGCGGAGGGA	CCAAGGTGGA	GATCAAA	

**L35 (SEQ ID NO:69)**

AATTTTATG	CTGACTCAGC	CCCACTCTGT	GTCCGGCGTCT	CCGGGGAAGA	CGGTACCAT	CTCCTGCACC
CGCAGCAGTG	GCGACATTGA	CAACAACAT	GTGCAGTGGT	ACCAGCAGCG	CCCGGGCAAT	TCCCCACCA
ATGTGATTTA	TGAGGATAAC	CGAAGACCC	CTGGGGTCCC	GGATCGCTTC	TCTGGCTCCA	TCGACAGCTC
CTCCAACCTC	GCCTCCCTCA	CCATCTCTGG	ACTGCAGCCT	GAGGACGAGG	CTGACTACTA	TTGTCACTCT
TATCAAAGCG	ACAATTGGGT	GTTCGGCGGA	GGGACCAAGG	TGACCGTCCT	A	

**L36 (SEQ ID NO:71)**

AATTTTATG	CTGACTCAGC	CCCACTCTGT	GTCCGGAGTCT	CCGGGGAAGA	CGGTACCAT	CTCCTGCACC
CGCAGCAGTG	GCAGCATTCG	CAGCAACTAT	GTGCAGTGGT	ACCAGCAGCG	CCCGGGCAGT	TCCCCACCA
CTGTGATCTA	TGAGGATAAC	CAAAGACCC	CTGGGGTCCC	TGATCGATTTC	TCTGGCTCCA	TCGACAGCTC
CTCCAACCTC	GCCTCCCTCA	CCATCTCTGG	ACTGAAGACT	GAGGACGAGG	CTGACTACTA	CTGTCACTCT
TATGATAGCA	GCAATGTGGT	GTTCGGCGGA	GGGACCAAGC	TGACCGTCCT	A	

**L37 (SEQ ID NO:73)**

GATGTTGTGA TGACTCAGTC TCCACTCTCC CTGCCCCGTC CCCCTGGGGA GCCGGCCTCC ATCTCCTGCA  
 GGTCTAGTCA GAGCCTCCTG CATAGTAATG GATACAAC TAATTGGATTGG TACCTGCAGA AGCCAGGGCA  
 GTCTCCACAG CTCTTGATCT ATTTGGGTTT TAACCGGGAC TCTGGGGTCC CAGACAGATT CAGCGGCAGT  
 GGGTCAGGCA CTGATTTCAC ACTGAAAATC AGCAGGGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA  
 TGCAAGGTAC AACTGGCCG TACACTTTTG GCCAGGGGAC CAGGCTGGAG ATCAAA

**L38 (SEQ ID NO:75)**

GATGTTGT GATGACTCAG TCTCCACTCT CCCTGCCCGT CACCCCTGGA GAGTCGGCCT CCATCTCCTG  
 CAGGTCTAGT CAGAGCCTCC TGCATAGTAA TGGATACAAC TTTTGGATT GGTACCTGCA GAAGCCAGGG  
 CAGTCTCCAC AGCTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG TTCAGTGGCA  
 GTGGATCAGG CACAGATTTT AACTGAAAA TCAGCAGAGT GGAGGCTGAG GATGTTGGGG TTTATTACTG  
 CATCAAGCT CTACAACTC CTCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA

**L39 (SEQ ID NO:77)**

GA TGTGTGATG ACTCAGTCTC CACTCTCCCT GCCCGTCACC CCTGGAGAGC CGGCCTCCAT  
 CTCCTGCAGG TCTAGTCAGA GCCTCCTGCA TAGTAATGGA TACAACATT TGGATTGGTA CCTGCAGAAG  
 CCAGGGCAGT CTCCACAGCT CCTGATCTAT TTGGGTCTTA ATCGGGCCTC CGGGGTCCCT GACAGGTTCA  
 GTGGCAGTGG ATCAGGCACA GATTTTACAC TGAAAATCAG CAGAGTGGAG GCTGAGGATG TTGGGGTTTA  
 TTACTGCATG CAAGCTCTAC AAACCCCCCT CACTTTCGGC GGAGGGACCA AGGTGGAGAT CAAA

**L40 (SEQ ID NO:79)**

GAAACGAC ACTCAGCAG TCTCCAGCCA CCCTGTCTTT GTCTCCAGGG CAAAGAGCCA CCCTCTCCTG  
 CAGGGCCAGT CAGAGTGTCT ACAACTACTT AGCCTGGTAC CAACAGAAGC CTGGCCAGGC TCCCAGGCTC  
 CTCATCTATG ATGCATCCAG AAGGGCAACT GGCATCCAG CCAGGTTTCA TGGCAGTGGG TCTGGGACAG  
 ACTTCACTCT CACCATCAGC AGCCTAGAGC CTGAAGATTT TGCAGTTTAT TACTGTCAGC AGCGTAACAA  
 CTGCCCCTC ACTTTCGGTG GAGGGACCAA GGTGGAGATC AAA

**L41 (SEQ ID NO:81)**

GACAT CCAGTTGACC CAGTCTCCAT CCTCCCTGTC TGCTTCTGTT GGAGACAGCG TCACCATCTC  
 TTGCCGGGCA AGTCAGAGTC CTGGCATCTT TTTAAATTGG TATCAGCAGA TACCAGGGAA AGCCCCATAA  
 CTCCTGATCT ACGCTACATC CACTCTGGAA AGTGGGGTCC CCCCAGGTT CACCGGCAGT GGATCTGGGA  
 CAGATTTTAC TCTCACCATC AGCAGTCTGC AACCTGAGGA CTTTGCAACT TACTACTGTC AACAGAGTAA  
 CAGTGTTCGG CTCACTTTCG GCGGCGGGAC CAAGGTGGAG ATCAAA

**L42 (SEQ ID NO:83)**

GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC  
 CTGCAGGTCT AGTCAGAGCC TCCTGCATAG TAATGGATAC AACTATTTGG ATTTGGTACCT GCAGAAGCCA  
 GGGCAGTCTC CACAGCTCCT GATCTATTTG GGTCTTAATC GGGCCTCCGG GGTCCCTGAC AGGTTTCAGTG  
 GCAGTGGATC AGGCACAGAT TTTACACTAA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA  
 CTGCATGCAA GCTCTACAAA CTCCTCTAAC CTTGCGGCCAA GGGACACGAC TGGAGATTAA A

**L43 (SEQ ID NO:85)**

GAAATT GTGATGACGC AGTCTCCAGC CACCCTGTCT GTGTCTCCAG GGGAAAGAGC CACCTTCTCC  
 TGTAGGGCCA GTCAGAGTGT TGGCAGCAAC TTAGCCTGGT ACCAGCAGAA ACCTGGCCAG GCTCCCAGGC  
 TCCTCATCTA TGATGCATCC AACAGGGCCA CTGGCATCCC AGCCAGGTTT AGTGGCAGTG GGTCCTGGAC  
 AGACTTCACT CTCACCATCA GCAGACTGGA GCCTGAAGAT TTTGCAGTGT ATTACTGTCA GCAGCGTAGC  
 AACTGGCCCC TCACTTTCGG CGGAGGGACC AAGGTGGAGA TCAAA

**L44 (SEQ ID NO:87)**

GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC  
 CTGCAGGTCT AGTCAGAGCC TCCTGCATAG TAATGGATAC AACTATTTGG ATTTGGTACCT GCAGAAGCCA  
 GGGCAGTCTC CACAGCTCCT GATCTATTTG GGTCTTAATC GGGCCTCCGG GGTCCCTGAC AGGTTTCAGTG  
 GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA  
 CTGCATGCAA GCTCTACAAA CTCCTCTAAC TTTGCGCGGA GGGACCAAGG TGGAGATCAA A

**L45 (SEQ ID NO:89)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCGTCACCC CTGGAGAGCC GGCCTCCATC  
 TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC  
 CAGGGCAGT TCCACAGCTC CTGATCTACT TGGGTCTTAC TCGGGCCTCC GCGTCCCTG ACAGGTTTCA  
 TGGCAGTGGG TCAGGCACAG ATTTTCACT GAAAATCAGC AGATGGAGG CTGAGGATGT TGGGGTTTAT  
 TACTGCATGC AAGCTCTACA AACTCCTTAC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

**L46 (SEQ ID NO:91)**

GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC  
 CTGCAGGTCT AGTCAGAGCC TCCTGCATAG TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA  
 GGGCAGTCTC CACAGCTCCT GATCTATTTG GGTTCATAATC GGGCCTCCGG GGTCCCTGAC AGGTTCACTG  
 GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA  
 CTGCATGCAA GCTCTACAAA CTCCCTCACC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A

**L47 (SEQ ID NO:93)**

GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC  
 CTGCAGGTCT AGTCAGAGCC TCCTGCATAG TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA  
 GGGCAGTCTC CACGGCTCCT GATCTATTTG GGTTCATAATC GGGCCTCCGG GGTCCCTGAC AGGTTCACTG  
 GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA  
 CTGTATGCAA GGTCTACAAA CTCCCTCACC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A

**L48 (SEQ ID NO:95)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCTGGAG AGCCGGCCTC CATCTCCTGC  
 AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAAT AATTGGATTG GTACCTGCAG AAGCCAGGGC  
 AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG  
 TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGGGTG GAGGCTGAGG ATGTTGGGGT TTATTATTGC  
 ATGCAAGCTA CACACTGGCC GTACACTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA

**L49 (SEQ ID NO:97)**

AATTTTA TGCTGACTCA GCGCCACTCT GTGTCCGAGT CTCCGGGGAA GACGGTAAGC ATCTCCTGCA  
 CCCGCAACAG TGGCAGCATT GCCAGCAACT TTGTGCAGTG GTACCAGCAG CGCCCGGGCA GTGCCCCAC  
 CATTGTAATC TATGAGGATA ACCAAAGACC CTCTGCGGTC CTTACTCGGT TCTCTGGCTC CATCGACAGG  
 TCCTCCAACCT CTGCCCTCCT CACCATCTCT GGAAGTACGA CTGAGGACGA GGCTGACTAC TACTGTCACT  
 CTTATGATAG CGCCAATGTC ATTTTCGGCG GGGGGACCAA GCTGACCGTC CTA

**L50 (SEQ ID NO:99)**

GAAACG AACTCAGC AGTCTCCAGG CACCCTGTCT TTGTCTCCAG GGGAGAGAGC CACCCTCTCC  
 TGCAGGGCCA GTGAGACTAT CAGCAGCAGC CACTTAGCCT GGTACCAGCA GAAACCTGGC CAGTCTCCCA  
 GGCTCCTCAT CTATGGTGCG GGCTACAGGG CCACCGGCAT TCCAGACAGG TTCAGTGGCA GTGGGTCTGG  
 CACAGACTTC ACTCTCACCA TCAGCAGACT GGAGCCTGAA GATTTTGCAG TGTATTACTG TCAGCACTAT  
 GGTAGTTCAC TCCGGACGTT CGGCCAAGGG ACCAAGGTGG AAATCAAA

**L51 (SEQ ID NO:101)**

AATTTT ATGCTGACTC AGCCCACTC TGTGTCCGAG TCTCCGGGGA AGACGGTAAC CATCTCCTGC  
 ACCGGCAGCG GTGGCAACAT TGCCAGCAAT TATGTGCAGT GGTACCAGCA GCGCCCGGGC AGGGCCCCCA  
 CCACTGTGAT CTATGAGGAT AATCGAAGAC CCTCTGGGGT CCCTGATCGG TTCTCTGGCT CCATCGACAG  
 CTCTCCAAC TCTGCCTCCC TCACCATCTC TGGACTGAAG ACTGAAGACG AGGCTGACTA CTACTGTGAG  
 TCTTATGATC CCTACAATCG AGTGTTCGGC GGAGGGACCA AGCTGACCGT CTA

**L51 (SEQ ID NO:103)**

GAAA TTGTGATGAC GCAGTCTCCA CTCTCCCTGC CCGTCACCCC TGGAGAGCCG GCCTCCATCT  
 CCTGCAGGTC TAGTCAGAGC CTCCTGCATA CTAATGGATA CGACTATTTG GATTGGTACC TGCAGAAGCC  
 AGGGCAGTCT CCACAGCTTC TGATCTATTT GGGTTCTACT CGGGCCTCCG GGTCCCTGA CAGGTTCACT  
 GGCAGTGGAT CGGGCACAGA TTTTACACTG AAAATCAGCA GAGTGGAGGC TGAGGATGTT GGGGTTTATT  
 ACTGCATGCA AGCTTTTCAA ACTCCGCTCA CTTTCGGCGG AGGGACCAAG ATGGAGATCA AA

**H1 (SEQ ID NO:105)**

GAGGTGCAGC TGGTGGAGAC CGGCCCAGGA CTGGTGAAGC CTTCCGGGGAC CTTGTCCCTC ACCTGCGCTG  
 TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCAGGGA AGGGGCTGGA  
 GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCTGCC TCAAGAGTCG AGTCACCATA  
 TCAGTAGACA AGTCCAAGAA CCAGTCTCC CTGAAGCTGA GCTCTGTGAC CGCCCGGGAC ACGGCCGTGT  
 ATTACTGTGC GAGATTTAAT TACTATGATA GTAGTGTCTG GGGCCAGGGA ACCCTGGTCA CCGTCTCAAG  
 C

**H2 (SEQ ID NO:107)**

GAGGTGCAGC TGGTGGAGAC CGGCCCAGGA CTGGTGAAGC CTTCCGGGGAC CTTGTCCCTC ACCTGCGCTG  
 TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCAGGGA AGGGGCTGGA  
 GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCTGCC TCAAGAGTCG AGTCACCATA  
 TCAGTAGACA AGTCCAAGAA CCAGTCTCC CTGAAGCTGA GCTCTGTGAC CGCCCGGGAC ACGGCCGTGT  
 ATTACTGTGC GAGAGGGGTT GAGCAGATTG ACTACTGGGG CCAGGGAACC CTTGTCAACC TCTCAAGC

**H3 (SEQ ID NO:109)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCCGGGGAC CTTGTCCCTC ACCTGCGCTG  
 TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCAGGGA AGGGGCTGGA  
 GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCTGCC TCAAGAGTCG AGTCACCATA



TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC TGCCGCGGAC ACGGCCGTGT  
ATTACTGTGC GAAAAATTTA GCAGCAGGGG CCGTTGCCTA CTGGGGCCAG GGCACCCCTGG TCACCGTCTC  
AAGC

**H4 (SEQ ID NO:111)**

CAGGTGCAG CTACAGCAGT GGGGCGCAGG ACTGTTGAAG CCTTCGGAGA CCCTGTCCCT CACCTGCGCT  
GTCTCTGGTG GGTCCCTTCAG TGGTTACTAC TGGAGCTGGA TCCGTCAGCC CCCAGGGAAG GGGCTGGAGT  
GGATTGGGGA AATCAATCAT AGTGGAAGTA CCAACTACAA CCGGTCCCTC AAGAGTCGAG TCACCATATC  
AGTAGACACG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CCGCGGACAC GGCTGTGTAT  
TACTGTGCGA GACTTTCATA TGGTTCGGGC GTTGACTACT GGGGCCAGGG CACCCTGGTC ACCGTCTCAA  
GC

**H5 (SEQ ID NO:113)**

C AGCTGCAGCT GCAGGAGTCG GGCCAGGAC TGGTGAAGCC TTCACAGACC CTGTCCCTCA  
CCTGCACTGT CTCTGGTGGC TCCATCAGCA GTAGTAAGTG GTGGAGTTGG GTCCGCCAGC CCCAGGGAA  
GGGGCTGGAG TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAAGTACA ACCCGTCCCT CAAGAGTCGA  
GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGCGGACA  
CGGCCGTGTA TTAAGTGTGC AGGTATAGCA GCAGCCGCAA TGATGCTTTT GATATCTGGG GCCAAGGGAC  
AATGGTCACC GTCTCAAGC

**H6 (SEQ ID NO:115)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG  
TCTCTGGTGG CTCCATCAGC AGTAGTAAGT GGTGGAGTTG GTCCGCCAGC CCCCAGGGA AGGGGCTGGA  
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCTGCC TCAAGAGTCG AGTCACCATA  
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT  
ATTACTGTGC GAGAGATGGG CAGCTGGATG CTTTTGATAT CTGGGGCCAA GGGACAATGG TCACCGTCTC  
AAGC

**H7 (SEQ ID NO:117)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG  
TCTCTGGTGG CTCCATCAGC AGTAGTAAGT GGTGGAGTTG GTCCGCCAGC CCCCAGGGA AGGGGCTGGA  
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCTGCC TCAAGAGTCG AGTCACCATA  
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT  
ATTACTGTGC GAGATTTTGG GACTACTACG GTATGGACGT CTGGGGCCAA GGGACCACGG TCACCGTCTC  
AAGC

**H8 (SEQ ID NO:119)**

CAGGTG CAGCTACAGC AGTGGGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC  
GCTGCTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGG GTTGGGTCCG CCAGCCCCCA GGAAGGGGC  
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCGAGA GTCGAGTCAC  
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC AGACACGGCC  
GTGTATTACT GTGCGAGAGA TCGGTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT  
CAAGC

**H9 (SEQ ID NO:121)**

G AGGTGCAGCT GGTGAGTCT GGCCAGGAC TGGTGAAGCC TTCGGGGACC CTGTCCCTCA  
CCTGCGCTGT CTCTGGTGGC TCCATCAGCA GTAGTAAGTG GTGGAGTTGG GTCCGCCAGC CCCAGGGAA  
GGGGCTGGAG TGGATTGGGT ACATCTATTA TAGTGGGAGC ACCTACTACA ACCCGTCCCT CAAGAGTCGA  
GTCACCATGT CAGTAGACAC GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGAGACA  
CGCCCGTGTA TTAAGTGTGC AGATGGAGCT ACTTGGATGC TTTTGATATC TGGGGCCAAG GGACAATGGT  
CACCGTCTCA AGC

**H10 (SEQ ID NO:123)**

GAGGTGC AGCTGGTGGG GTCTGGCCCA GGAAGTGGTG AGCCTTCGGG GACCCTGTCC CTCACCTGCG  
CTGTCTCTGG TGGCTCCATC AGCAGTAGTA ACTGGTGGAG TTGGGTCCGC CAGCCCCCAG GGAAGGGGCT  
GGAGTGGATT GGGGAAATCT ATCATAGTGG GAGCACCAAC TACAACCCGT CCCTCAAGAG TCGAGTCACC  
ATATCAGTAG ACAAGTCCAA GAACCAAGTTC TCCCTGAAGC TGAGCTCTGT GACCCTGCGG GACACGGCCG  
TGTATTACTG TGCGAGAGAT TACGATATTT TCGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTACCGGT  
CTCAAGC

**H11 (SEQ ID NO:125)**

CAGCT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG GGGACCCTGT CCCTCACCTG  
CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG  
CTGGAGTGGG TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG AGTCGAGTCA  
CCATATCAGT AGACAAGTCC AAGAACCAGT CCTCCCTGAA GCTGAGCTCT GTGACCGCCG CGGACACGGC

CGTGTATTAC TGTGCGAGAG CCAACAGAGA TGATGCTTTT GATATCTGGG GCCAAGGGAC AATGGTCACC  
GTCTCAAGC

**H12 (SEQ ID NO:127)**

GAGGTGC AGCTGGTGGG GTCTGGGGGA GGCTTGGTAC AGCCGGGGGG GTCCCTGAGA CTCTCCTGTG  
CAGCCTCTGG ATTCACCTTT AGCAGCTATG CCATGAGCTG GGTCCGCCAG GCTCCAGGGA AGGGGCTGGA  
GTGGGTCTCA GCTATTAGTG GTAGTGGTGG TAGCACATAC TACGCAGACT CCGTGAAGGG CCGGTTCACC  
ATCTCCAGAG ACAATTCCAA GAACACGCTG TATCTGCAA TGAACAGTCT GAGCGCCGAC GACACGGCCG  
TATATTCTG TCGCTCGGGT GGCTGGTACG GGGACTACTT TGACTACTGG GGCCAGGGAA CCCTGGTCAAC  
CGTCTCAAGC

**H13 (SEQ ID NO:129)**

CAGGTGCAGC TGCAGGAGTC CGGCCAGGA CTGGTGAAGC CTTCCGAGAC CCTGTCCCTC ACCTGCACTG  
TCTCTGGTGG CTCCATCAGC AGTAGTAAC TGGTGGAGTT GGTCCGCCAG CCCCAGGGA AGGGGCTGGA  
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA  
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT  
ATTACTGTGC GAGAGAAGGG AACCGAACGG TGAAGTAGTC TTTTGATATC TGGGGCCAAG GGACAATGGT  
CACCGTCTCA AGC

**H14 (SEQ ID NO:131)**

CAGGTGCA GCTGCAGGAG TCCGGCCAG GACTGGTGAA GCCTTCGGGG ACCCTGTCCC TCACCTGCGC  
TGTCTCTGGT GGTCCATCA GCAGTAGTAA CTGGTGGAGT TGGGTCCGCC AGCCCCAGG GAAGGGGCTG  
GAGTGGATTG GGGAAATCTA TCATAGTGGG AGCACCAACT ACAACCCGTC CCTCAAGAGT CGAGTCACCA  
TATCAGTAGA CAAGTCCAAG AACAGTTCT CCCTGAAGCT GAGCTCTGTG ACCGCTGCGG ACACGGCCGT  
GTACTACTGT GCGAGAGGGC TGGGGGATAG TAGTGGTTAT ATCCTTTGGG GCCAAGGGAC AATGGTCACC  
GTCTCAAGC

**H15 (SEQ ID NO:133)**

CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC  
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGG GTTGGGTCCG CCAGCCCCCA GGGGAAGGGG  
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCTGC GGACACGGCC  
GTGTACTACT GTGCGAGAGG GCTGGGGGAT AGTAGTGGTT ATATCCTTTG GGGCCAAGGG ACAATGGTCA  
CCGTCTCAAG C

**H16 (SEQ ID NO:135)**

CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC  
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGG GTTGGGTCCG CCAGCCCCCA GGGGAAGGGG  
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCC  
GTGTATTACT GTGCGAGATG GACCGGGCGT ACTGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA  
CCGTCTCAAG C

**H17 (SEQ ID NO:137)**

CAGG TGCAGCTGCA GGAGTCCGGC CCAGGACTGG TGAAGCCTTC GGGGACCCTG TCCCTCACCT  
GCGTGTCTC TGGTGGCTCC ATCAGCAGTA GTAAGTGGTG GAGTTGGGTC CGCCAGCCCC CAGGGAAGGG  
GCTGGAGTGG ATTGGGGAAA TCTATCATAG TGGGAGCACC AACTACAACC CGTCCCTCAA GAGTCGAGTC  
ACCATATCAG TAGACAAGTC CAAGAACCAG TTCTCCCTGA AGCTGAGCTC TGTGACCGCC GCGACACCGG  
CCGTGTATTA CTGTGCGAGA CAAGGGGCGT TAGATGCTTT TGATATCTGG GGCCAAGGGA CCACGGTCAC  
CGTCTCAAGC

**H18 (SEQ ID NO:139)**

GCAGCTGGTG GAGTCCGGGG GAGGCGTGGT CCGACCTGGG GGGTCCCTGA GACTCTCCTG TGCAGCGTCT  
GGATTACCT TTAGCAGCTA TGCCATGAGC TGGGTCCGCC AGGCTCCAGG GAAGGGGCTG GAGTGGGTCT  
CAACTATTAG TGGTAGTGGT GGTAGCACAT ACTACGCAGA CTCCGTGAAG GGCCGGTTCA CCATCTCCAG  
AGACAATTCC AAGAACACGC TGTATCTGCA GATGAACAGC CTGAGAGCCG AGGACACGGC CGTATATTAC  
TGTGCGAAAG AGCGTGGCAG TGGCTGGTCC TTAGACAATA TGGACGTCTG GGGCCAAGGG ACCACGGTCA  
CCGTCTCAAG C

**H19 (SEQ ID NO:141)**

CAGGTGCAGC TGGTGGAGTC TGGCCCAGGA CTGGTGAAGC CTTCCGGGAC CCTGTCCCTC ACCTGCGCTG  
TCTCTGGTGG CTCCATCAGC AGTAGTAAC TGGTGGAGTT GGTCCGCCAG CCCCAGGGA AGGGGCTGGA  
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA  
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCTGCGGAC ACGGCCGTGT  
ATTACTGTGC GAGAGATAGC AGTGGGTTCT ACGGTATGGA CGTCTGGGGC CAAGGGACCA CCGTCACCGT  
CTCAAGC

**H20 (SEQ ID NO:143)**

CAGGTG CAGCTGCAGG AGTCGGGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC  
 GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGGAAGGGGC  
 TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
 CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACTGCCGC GGACACGGCC  
 GTGTATTACT GTGCGAGAAG CAGCAGCTGG TACTGGAATG CTTTGTATAT CTGGGGCCAA GGGACAATGG  
 TCACCGTCTC AAGC

**H21 (SEQ ID NO:145)**

CAGGTG CAGCTACAGC AGTGGGGCCC AGCACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC  
 TCTGTCTCTG GTGTCTCCAT CACCAGTAAT ATCTGGTGGA GTTGGGTCCG CCAGTCCCCA GGGGAAGGGGC  
 TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
 CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCT  
 GTGTATTACT GTGCGGGGTA CCGTAGCTTC GGGGAGTCCT ACTGGGGCCA GGGGAACCTG GTCACCGTCT  
 CAAGC

**H22 (SEQ ID NO:147)**

CAGGTGCA GCTACAGCAG TGGGGCGCAG GGCTGTTGAA GCCTTCGGAG ACCCTGTCTC TCACCTGCGT  
 TGCTATGGT GGGTCCCTCA CCGATTCTTA CTGGAGCTGG ATCCGCCAGC CCCCAGGGAA GGGGCCAGAG  
 TGGATTGGGG AAGTCAATCC TAGAGGAAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA GCCACCATAT  
 CACTAGACAC GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG TTCTGTGACC GCCGCGGACA CGGCTGTGTA  
 TTTCTGTGCG AGAGGTCTCT GGGCCGGGAG AGATGGCTAC AATTACTTTG ACAACTGGGG CCAGGGCACC  
 CTGGTCAACG TCTCAAGC

**H23 (SEQ ID NO:149)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC CCTGTCCCTC ACCTGCACTG  
 TCTCTGGTGG CTCCATCAGC AGTAGTAAC TGTGGAGTTG GGTCCGCCAG CCCCAGGGA AGGGGCTGGA  
 GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA  
 TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT  
 ATTACTGTGC GAGAGGTATA GCAGCAGCTG GTCAAGGTGA CTACTGGGGC CAGGGAACCC TGGTCAACCGT  
 CTCAAGC

**H24 (SEQ ID NO:151)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC CCTGTCCCTC ACCTGCACTG  
 TCTCTGGTGG CTCCATCAGC AGTAGTAGTT ACTACTGGGG CTGGATCCGC CAGCCCCCAG GGAAGGGGCT  
 GGAGTGGATT GGGAGTATCT ATTATAGTGG GAGCACCTAC TACAACCCGT CCCTCAAGAG TCGAGTCACC  
 ATATCCGTAG ACACGTCCAA GAACCAAGTT TCCCTGAAGC TGAGCTCTGT GACCCGCGCG GACACGGCCG  
 TGTATTACTG TGCGAGAGAT GGGGGATACT ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  
 CACCGTCTCA AGC

**H25 (SEQ ID NO:153)**

CAGGTG CAGCTGCAGG AGTCGGGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC  
 GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGGAAGGGGC  
 TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
 CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCC  
 GTGTATTACT GTGCGAGTAG TGGTTATGAT GCTTTTGATA TCTGGGGCCA AGGGACCACG GTCACCGTCT  
 CAAGC

**H26 (SEQ ID NO:155)**

CAGGT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG GGGACCCTGT CCCTCACCTG  
 CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG TAATTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG  
 CTGGAGTGGG TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG AGTCGAGTCA  
 CCATATCAGT AGACAAGTCC AAGAACCAGT TCTCCCTGAA GCTGAGCTCT GTGACCGCCG CGGACACGGC  
 CGTGTATTAC TGTGCACGAT ACAGCTATGG AACGGTAGGA ATTGACTACT GGGGCCAGGG AACCTTGGTC  
 ACCGTCTCAA GC

**H27 (SEQ ID NO:157)**

GAGGT GCAGCTGGTG CAGTCTGGGG GAGGCGTGGT CCAGCCTGGG ACGTCCCTGA GACTCTCCTG  
 TGCAGCCTCT GGATTCAGCT TCAGAAGTCA TGGCATGCAC TGGGTCCGCC AGGCTCCAGG CAAGGGGCTG  
 GAGTGGGTGG CAGTTATATC ATATGATGGA AGTAATAAAT ACTATGCAGA CTCCGTGAAG GCCCGATTCA  
 CCATCTCCAG AGACAATTCC AAGAACACGC TGTATCTGCA AATGAACAGC CTGAGAGCTG AGGACACGGC  
 TGTGTATTAC TGTGCGACTA TAGGGCCGGG GGGATTTGAC TACTGGGGCC AGGGCACCTT GGTACCGTCT  
 TCAAGC

**H28 (SEQ ID NO:159)**

CAG GTGCAGCTGC AGGAGTCCGG CCCAGGACTG GTGAAGCCTT CGGAGACCCCT GTCCCTCACC  
 TGCACGTCTCT CTGGTGGCTC CATTAGAAAT TACTACTGGA GTTGGATCCG GCAGCCCCCA GGGGAAGGGAC  
 TGGAGTGGAT TGGGTATAT TCTGACAGTG GGAATACCAA CTACAATCCC TCCCTCAAGA GTCGAGTCAC  
 CATATCAGTA GACACGTCCA AGAACCAGTT CTCCCTAAAG CTGACCTCTG TGACCGCCAC AGACACGGCT  
 GCGTATTTCT GTGCGAGACA TCGAAGCAGC TGGGCATGGT ACTTCGATCT CTGGGGCCGT GGCACCCTGG  
 TCACCGTCTC AAGC

**H29 (SEQ ID NO:161)**

C AGGTGCAGCT GCAGGAGTCG GGCCAGGAC TGGTGAAGCC TTCGGAGACC CTGTCCCTCA  
 CCTGCGCTGT CTCTGGTGGC TCCATCAGCA GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA  
 GGGGCTGGAG TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA  
 GTCAACATAT CATTAGACAA GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGCGGACA  
 CGGCCGTGTA TTACTGTGCG AGAGTGGGCA GTGGCTGGTA CGTTGACTAC TGGGGCCAGG GAACCTGGT  
 CACCGTCTCA AGC

**H30 (SEQ ID NO:163)**

CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG GGACCTGTC CCTCACCTGC  
 GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGG GTTGGGTCCG CCAGCCCCCA GGGGAAGGGGC  
 TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
 CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCG GCACACGGCC  
 GTGTATTACT GTGCGAGAGT TTCTGGCTAC TACTACTACG GTATGGACGT CTGGGGCCAA GGGACCACGG  
 TCACCGTCTC AAGC

**H31 (SEQ ID NO:165)**

GAGGTCCA GCTGGTACAG TCTGGGGGAG GCGTGGTCCA GCCTGGGAGG TCCCTGAGAC TCTCCTGTGC  
 AGCCTCTGGA TTCACCTTCA GTAGCTATGG CATGCACTGG GTCCGCCAGG CTCCAGGCAA GGGGCTGGAG  
 TGGGTGGCAG TTATATCATA TGATGGAAGT AATAAATACT ATGCAGACTC CGTGAAGGGC CGATTACCA  
 TCTCCAGAGA CAATTCCAAG AACACGCTGT ATCTGCAAAT GAACAGCCTG AGAGCTGAGG ACACGGCTGT  
 GTATTACTGT GCGAAAGCGT ATAGCAGTGG CTGGTACGAC TACTACGGTA TGGACGTCTG GGGCCAAGGG  
 ACCACGGTCA CCGTCTCAAG C

**H32 (SEQ ID NO:167)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG  
 TCTCTGGTGG CTCCATCAGC AGTAGTAAC TGGTGGAGTTG GTCCGCCAG CCCCAGGGA AGGGGCTGGG  
 GTGGATTTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA  
 TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT  
 ATTACTGTGC GAGAGCCAGC GTTGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA CCGTCTCAAG  
 C

**H33 (SEQ ID NO:169)**

CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG GGACCTGTC CCTCACCTGC  
 GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGG GTTGGGTCCG CCAGCCCCCA GGGGAAGGGGC  
 TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
 CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCTGC GGACACGGCC  
 GTGTACTACT GTGCGAGAGG GCTGGGGGAT AGTAGTGGTT ATATCCTTTG GGGCCAAGGG ACAATGGTCA  
 CCGTCTCAAG C

**H34 (SEQ ID NO:171)**

CAGGTA CAGCTGCAGC AGTCAGGCCC AGGACTGGTG AAGCCTTCGG GGACCTGTC CCTCACCTGC  
 GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGG GTTGGGTCCG CCAGCCCCCA GGGGAAGGGGC  
 TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
 CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACTCCCGA GGACACGGCT  
 GTGTATTACT GTGCAAGAGA TCACGGCCCC TTTGACTACT GGGGCCGGGG AACCTGGTC ACCGTCTCAA  
 GC

**H35 (SEQ ID NO:173)**

CAGGT GCAGCTGGTG CAATCTGGGG GAGGCGTGGT CCAGCCTGGG AGGTCCCTGA GACTCTCCTG  
 TGCAGCCTCT GGATTCGCCCT TCAGTAGCTA TGGCATGCAC TGGGTCCGCC AGGCTCCAGG GAAGGGGCTG  
 GAGTGGGTTT CATACATTAG TAGTAGTAGT AGTACCATAI ACTACGCAGA CTCTGTGAAG GGCCGATTCA  
 CCACTCTCCAG AGACAATTCC AAGAACACGC TGTATCTGCA AATGAACAGC CTGAGAGCCG AGGACACGGC  
 TGTGTATTAC TGTGCGAGAG ATCGATTTGG GTCGGGGCAC TTGCCCGACT ACTGGGGCCA GGGGAACCTG  
 GTCACCGTCT CAAGC

**H36 (SEQ ID NO:175)**

CAGGT GCAGCTACAG CAGTGGGGCG CAGGACTGTT GAAGCCTTCG GAGACCCTGT CCCTCACCTG  
 CGCTGTCTAT GGTGGGTCCCT TCAGTGGTTA CTACTGGAGC TGGATCCGCC AGCCCCCAGG GAAGGGGGCTG  
 GAGTGGATTG GGGAAATCAA TCATAGTGGG AGCACCAACT ACAACCCGTC CCTCAAGAGT CGAGTCACCA  
 TATCAGTAGA CACGTCCAAG AACCAGTTCT CCCTGAAGCT GAGCTCTGTG ACCGCCGCGG ACACGGCTGT  
 GTATTACTGT GCGAGAGTTG GGTATAGCAG TGGCCGTGAC GTTGACTACT GGGGCCAGGG CACCCTGGTC  
 ACCGTCTCAA GC

**H37 (SEQ ID NO:177)**

GAGGTCC AGCTGGTGGG GTCTGGCCCA GGACTGGTGA AGCCTTCGGG GACCCTGTCC CTCACCTGCG  
 CTGTCTCTGG TGGCTCCATC AGCAGTAGTA ACTGGTGGAG TTGGATCCGG CAGCCCCCAG GGAAGGGGCT  
 GGAGTGGATT GGGGAAATCT ATCATAGTGG GAGACCAAC TACAACCCGT CCTCAAGAG TCGAGTCACC  
 ATATCAGTAG ACAAGTCCAA GAACCAGTTC TCCCTGAAGC TGAGCTCTGT GACCGCCGCG GACACGGCCG  
 TGTATTACTG TGCAGAGAGT AGCAGCAGCT GGTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  
 CACCGTCTCA AGC

**H38 (SEQ ID NO:179)**

GAGGT CCAGCTGGTG GAGTCCGGCC CAGGACTGGT GAAGCCTTCG GAGACCCTGT CCCTCACCTG  
 CGCTGTCTCT TGGTGGCTCCA TCAGCAGTAG TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG  
 CTGGAGTGGG TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG AGTCGAGTCA  
 CCATATCAGT AGACAAGTCC AAGAACCAGT TCTCCCTGAA GCTGAGCTCT GTGACCGCTG CGGACACGGC  
 CGTATATTAT TGTGCGAGAT CGACGTGGTC CCTTGACTAC TGGGGCCAGG GCACCCTGGT CACCGTCTCA  
 AGC

**H39 (SEQ ID NO:181)**

GAGGTCCAG CTGGTGGAGT CTGGCCAGG ACTGGTGAAG CCTTCGGGGA CCCTGTCCCT CACCTGCGCT  
 GTCTCTGGTG GCTCCATCAG CAGTAGTAAC TGGTGGAGTT GGTCCGCCA GCCCCAGGG AAGGGGCTGG  
 AGTGGATTGG GGAAATCTAT CATAGTGGGA GCACCAACTA CAACCCGTCC CTCAAGAGTC GAGTCACCAT  
 ATCAGTAGAC AAGTCCAAGA ACCAGTTCTC CCTGAAGCTG AGCTCTGTGA CCGCTGCGGA CACGGCCGTA  
 TATTACTGTG CGAGACTCTC GTTTGCCGAT CCTTTTGATA TCTGGGGCCA AGGGACAATG GTCACCGTCT  
 CAAGC

**H40 (SEQ ID NO:183)**

CAGGTCCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGTCCCTC GGTGAAGGTC TCCTGCAAGG  
 CTTCTGGAGG CACCTTCAGC AGCTATGCTA TCAGCTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG  
 GATGGGAAGG ATCATCCCCA TCCTTGGTAT AGCAAACCTAC GCACAGAAGT TCCAGGGCAG AGTCACGATT  
 ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGA GCAGCCTGAG ATCTGAGGAC ACGGCCGTGT  
 ATTACTGTGC ATATGGTTTCG GGGAGTTATT ACGACTACTA CTACATGGAC GTCTGGGGCA AAGGGACCAC  
 GGTACCCGTC TCAAGC

**H41 (SEQ ID NO:185)**

GAGGTCC AGCTGGTGCA GTCTGGGGGA GGCTTGGTCC AGCCTGGGGG GTCCCTGAGA CTCTCCTGTT  
 CAGCCTCCGG ATTCACCTTC AGTAGCTATG CTATGCACCTG GGTCCGCCAG GCTCCAGGGA AGGGACTGGA  
 ATATGTTTCA ACTATTAGTA GTAATGGGGA TAGCACATAC TACGCAGACT CCGTGAAGGG CAGATTACAC  
 ATCTCCAGAG ACAATTCCAA GAACACGCTG TATCTGCAAA TGAACAGCCT GAGAGCTGAG GACACGGCTG  
 TGTATTACTG TGCAGAAAGAA GAAGTATGGC TACAGGCTTT TGATATCTGG GGCCAAGGGA CAATGGTCAAC  
 CGTCTCAAGC

**H42 (SEQ ID NO:187)**

CA GCTGCAGCTG CAGGAGTCGG GCCCAGGACT GGTGAAGCCT TCGGAGACCC TGTCCCTCAC  
 CTGCACTGTC TCTGGTGGCT CCATCAGTAG TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG  
 CTGGAGTGGG TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC CTCCCTCAAG AGTCGAGTCA  
 CCATCTCAGT AGACACGTCC AAGAACCAGT TCTCCCTGAA GCTGAGCTCT GTGACCGCTG CGGACACGGC  
 CGTGATTATC TGTGCGAGAG ATAAGGGATA CATGGACGTC TGGGGCAAAG GGACCACGGT CACCGTCTCA  
 AGC

**H43 (SEQ ID NO:189)**

CAGGTACA GCTGCAGCAG TCAGGGGCTG AGGTGAAGAA GCCTGGGTCC TCGGTGAAGG TCTCCTGCAA  
 GGCTTCTGGA GGCACCTTCA GCAGCTATGC TATCAGCTGG GTGCGACAGG CCCCTGGACA AGGGCTTGAG  
 TGGATGGGAA GGATCATCCC TATCCTTGGT ATAGCAAAC ACGCACAGAA GTTCCAGGGC AGAGTCACGA  
 TTACCGCGGA CAAATCCACG AGCACAGCCT ACATGGAGCT GAGCAGCCTG AGATCTGAGG ACACGGCCGT  
 GTATTACTGT GCGAGAGATC ATAGGTTGCA CTACGCCTGG TACTTCGATC TCTGGGGCCG TGGCACCTG  
 GTCACCGTCT CAAGC

**H44 (SEQ ID NO:191)**

CA GGTGCAGCTG CAGGAGTCGG GCCCAGGACT GCTGAAGCCT TCGGGGACCC TGTCCCTCAC  
 CTGCGCTGTC TCTGGTGGCT CCATCAGCAG TAGCAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGGAG  
 GGGCTGGAGT GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC AAGAGTCGAG  
 TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CCGCGGACAC  
 GGCCGTCTAT TACTGTGCGA GAGATCTAAC GGGGAGTCTT GACTACTGGG GCCAGGGAAC CCTGGTCACC  
 GTCTCAAGC

**H45 (SEQ ID NO:193)**

CAGGTGCAGC TGCAGGAGTC CGGCCAGGA CTGGTGAAGC CTTCCGGGAC CCTGTCCCTC ACCTGCGCTG  
 TCTCTGGTGG CTCCATCAGC AGTAGTAAC TGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA  
 GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA  
 TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT  
 ATTACTGTGC GAGAATACGC TATGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA CCGTCTCAAG  
 C

**H46 (SEQ ID NO:195)**

CA GGTGCAGCTG CAGGAGTCGG GCCCAGGACT GGTGAAGCCT TCGGAGACCC TGTCCCTCAC  
 CTGCGCTGTC TCTGGTGGCT CCATCAGCAG TAGTAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGAAG  
 GGGCTGGAGT GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC AAGAGTCGAG  
 TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CTGCGGACAC  
 GGCCGTGTAT TACTGTGCCG TGACGGCAGC CCATGATGCT TTTGATATCT GGGGCCAAGG GACAATGGTC  
 ACCGTCTCAA GC

**H47 (SEQ ID NO:197)**

CA GGTGCAGCTA CAGCAGTGGG GCCCAGGACT GGTGAAGCCT TCGGGGACCC TGTCCCTCAC  
 CTGCGCTGTC TCTGGTGGCT CCATCAGCAG TAGTAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGAAG  
 GGGCTGGAGT GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC AAGAGTCGAG  
 TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CCGCGGACAC  
 GGCCGTGTAT TACTGTGCGA GAGACAGCAG TGGCCAAGGG TACTTTGACT ACTGGGGCCA GGGCACCTG  
 GTCACCGTCT CAAGC

**H48 (SEQ ID NO:199)**

GAGGTG CAGCTGGTGC AGTCTGGGGC TGAGGTGAAG AAGCCTGGGG CCTCAGTGAA GGTCTCCTGC  
 AAGGCTTCTG GATACACCTT CACTAGCTAT GCTATGCATT GGGTGCGCCA GGCCCCCGGA CAAAGGCTTG  
 AGTGGATGGG ATGGATCAAC GCTGGCAATG GTAACACAAA ATATTACAG AAGTTCCAGG GCAGAGTCAC  
 CATGACCAGG GACACGTCCA CGAGCACAGT CTACATGGAG CTGAGCAGCC TGAGATCTGA GGACACGGCC  
 GTGTATTACT GTGCTAGACA CTCGTACTAC TACGGTATGG ACGTCTGGGG CCAAGGCACC CTGGTCACCG  
 TCTCAAGC

**H49 (SEQ ID NO:201)**

CAG GTGCAGCTAC AGCAGTGGGG CGCAGGACTG TTGAAGCCTT CGGAGACCCT GTCCCTCACC  
 TGCGCTGTCT ATGGTGGGTC CTTCACTGGT TACTACTGGA GCTGGATCCG CCAGCCCCCA GGAAGGGGC  
 TGGAGTGGAT TGGGGAAATC AATCATAGTG GAAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC  
 CATATCGGTA GACAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCT  
 GTGTATTACT GTGCGAGAGT CGGGTATAGC CACGGCGAAG AAGTCTTGGG CGTCTGGGGC AAAGGGACCA  
 CGGTCACCGT CTCAAGC

**H50 (SEQ ID NO:203)**

CAGGT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG GAGACCCTGT CCCTCACCTG  
 CACTGTCTCT GGTGGCTCCA TCGGCAATTA TGACTGGAGT TGGATCCGGC AGCCCCCAGG GAAGGGACTG  
 GAGTGGATTG GGACTATCTA CTCTAGTGGG AGTACGTACT ACAGTCCGTC CCTCAAGAGT CGACTCACCA  
 TATCAGTAGA CAAGTCCAAG AACCGGTTCT CCCTGAAGCT GAGCTCTGTG ACCGCCCGG ACACGGCCGT  
 GTATTACTGT GCGAGAGCAC GAGGGTATAG CAGCCCCTTC GACCCCTGGG GCCAGGGCAC CCTGGTCACC  
 GTCTCAAGC

**H51 (SEQ ID NO:205)**

CA GGTCCAGCTG GTACAGTCTG GGGCTGAGGT GAAGAAGCCT GGGTCCTCGG TGAAGGTCTC  
 CTGCAAGGCT TCTGGAGGCA CCTTCAGCAG CTATGCTATC AGCTGGGTGC GACAGGCCCC TGGACAAGGG  
 CTTGAGTGGG TGGGAATAAT CAACCTAGT GGTGGTAGCA CAAGCTACGC ACAGAAGTTC CAGGGCAGAG  
 TCACCATTAC CAGGACACA TCCGCGAGCA CAGCCTACAT GGAGCTGAGC AGCCTGAGAT CTGAAGACAC  
 GGCTGTGTAT TACTGTGCGA GAGATCGGTG GAGGTACGAT GCTTTTGATA TCTGGGGCCA AGGGACAATG  
 GTCACCGTCT CAAGC

## H52 (SEQ ID NO:207)

G AGGTGCAGCT GGTGGAGTCT GGCCCAGGAC TGGTGAAGCC TTCGGGGACC CTGTCCCTCA  
CCTGCGCTGT CTCTGGTGGC TCCATCAGCA GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA  
GGGGCTGGAG TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA  
GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGCGGACA  
CGGCCGTGTA TTACTGTGCG AGAGAAAAAT CGGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTCACCGT  
CTCAAGC

Figure 2

LIGHT CHAIN VARIABLE REGION SEQUENCES

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4	SEQ ID NO		
L1	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKRLEIK	2	
L2	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKRLEIK	4	
L3	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	6	
L4	EIVLTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	8	
L5	EIVLTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVDIK	10	
L6	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	12	
L7	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	14	
L8	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	16	
L9	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKRLEIK	18	
L10	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	20	
L11	EIVLTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKRLEIK	22	
L12	NFMTLQPHSVSESGKIVT	ISCTHSSGSLASNYVQYQRP	SGVPSPTTIV	EDNR	RRPSGVPDR	FRSGSIDSSNSASLT	ISGLKTEDEADYYC	QSYDSSNQRFVFGGQTKLTVL	24	
L13	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	26	
L14	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	28	
L15	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKRLEIK	30	
L16	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	32	
L17	EIVLTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	34	
L18	DIQLTQSPSVASVGDVVT	ITCRASQGISRWLAWY	QOKPGAPRLLIY	AA	SGLQ	SGVPSRR	FRSGSGSGTDFTLT	ITSNLQPEDPATYYC	QQAASSFPITFGGQTKRLEIK	36
L19	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKLEIK	38	
L20	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVDIK	40	
L21	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKLEIK	42	
L22	SSELTQDPVAVSALGQIVR	ITCQGD	SLRTIYTGNYQOKPGQAPVLVLF	GKNRP	SGIPDR	FRSGSHSGNTASLT	ITGAQAEADYYC	NSRDI	TGVZFRFGGQTKLTVL	44
L23	EIVLTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	46	
L24	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	48	
L25	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVDIK	50	
L26	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	52	
L27	DIQLTQSPSLASVGDVVT	ITCRASQGISRWLAWY	QOKPGAPKLLIY	AA	STLQ	SGVPSRR	FRSGSGSGTDFTLT	ITSSIQPEDPATYYC	QQLNSVPLTFFGGQTKVEIK	54
L28	SVYLTQPPSVSVSPGQAS	ITC	SGDKLGDYVGVYQOKAGQA	PVLVIY	QDMKRP	SGITPER	FRSGNSGNTASLT	ISGTQAMDEADYYC	QAWDSGTVFGGQTKLTVL	56
L29	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	58	
L30	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	60	
L31	DIQLTQSPSLASVGDVVT	ITCRSSQGISRWLAWY	QOKPGAPKLLIY	AA	STLQ	SGVPSRR	FRSGSGSGTDFTLT	SINMLQPADPATYYC	QQSHSPPTVFGGQTKVEIK	62
L32	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	64	
L33	EIVLTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKLEIK	66	
L34	DVVTQSPSLPVTGPGEPA	ISCRSSQSLHSHSGNYNYLDWY	LQKPGQSPQLLIY	LGSNRA	SGVPDR	FRSGSGSGTDFTLK	ISRVEAEDVGYYC	MQALQTPITFGGQTKVEIK	68	
L35	NFMTLQPHSVSASPGKIVT	ISCTHSSGSLDNNYVQYQRP	PGNSPTNIV	EDNR	RRPSGVPDR	FRSGSIDSSNSASLT	ISGLQPEDEADYYC	QSYQSDNNWVFGGQTKVTVL	70	



L36	NFMLTQPHSVSESPGKTVTISC	TRSSGSLHSHNGYNYLDWYLQKPGSPQ	LLIYEDNQRPSPVDRFSGSIDSSNSASLT	ISGLKTEDEADYYCQSYDSSNVVFGG	GGTKLTVL	72		
L37	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOGTHWPTFFGQGRLEIK	74		
L38	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOALQTFPLFFGGGKVEIK	76		
L39	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOALQTFPLFFGGGKVEIK	78		
L40	ETTLTQSPATLSLSPGQ	RATLSCRASQSVINYILAWYQKPKQAPRL	LIYDASRATGIPARFSGSGSGTDF	TLTISLLEPEDFAVIYC	QQRNMWPLTFFGGGKVEIK	80		
L41	DIQLTQSPSLASVGD	SVTISCRAQSPGIFLAWYQKPKAPKLLIY	ATSTLES	GVPDRFSGSGSGTDF	TLTISLQPEDFAVIYC	QQSNSVPLTFFGGGKVEIK	82	
L42	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOALQTFPLFFGGGKVEIK	84		
L43	EIVMTQSPATLSVSPGER	ATFSCRASQSVGSINLAWYQKPKQAPRL	LIYDASNRATGIPARFSGSGSGTDF	TLTISRLEPEDFAVIYC	QQRNMWPLTFFGGGKVEIK	86		
L44	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOALQTFPLFFGGGKVEIK	88		
L45	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOALQTFPLFFGGGKVEIK	90		
L46	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOALQTFPLFFGGGKVEIK	92		
L47	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOGLQTFPLFFGGGKVEIK	94		
L48	DVVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOATHWPTFFGQGTKEIK	96		
L49	NFMLTQPHSVSESPGKTV	SVTISC	TRNSGSLASNFQWYQKPGSAPT	IVITYEDNQRPSPVDRFSGSIDSSNSASLT	ISGLTTEDEADYYCQSYDSSNVVFGG	GGTKLTVL	98	
L50	ETTLTQSPGTL	SLSPGERATLS	CRASQTFISSHLAWYQKPGSPQ	LLIY	GAGTRATGIPDRFSGSGSGTDF	TLTISRLEPEDFAVIYC	QOHTGSLRTRFGGKVEIK	100
L51	NFMLTQPHSVSESPGKTV	TVTISC	TGSGGNIASNYQWYQKPGRAP	TVITYEDNRPPSGVDRFSGSIDSSNSASLT	ISGLKTEDEADYYCQSYDPPYMRVFGG	GGTKLTVL	102	
L52	EIVMTQSPLSLPTPGEPA	SLSCRSSQSLHSHNGYNYLDWYLQKPGSPQ	LLIYLGSMNRASGVPDRFSGSGSGTDF	TLKISRVEADVGVIYC	MOAFQTFPLFFGGGKVEIK	104		

Figure 3

HEAVY CHAIN VARIABLE REGION SEQUENCES

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4	SEQ	ID
H1	EVQLVETGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	FNYYDS	SSWGQGLTVTVSS				106
H2	EVQLVETGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	GVQIDY	SSWGQGLTVTVSS				108
H3	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	KNLAAGAV	YWGQGLTVTVSS				110
H4	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	LSYGS	GVQIDYWGQGLTVTVSS				112
H5	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	YSSSR	DAFDIMWGQGLTVTVSS				114
H6	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	DGQLDA	FDIMWGQGLTVTVSS				116
H7	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	FNDY	YEMDYMWGQGLTVTVSS				118
H8	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	DRYTG	MDYMWGQGLTVTVSS				120
H9	EVQLVESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	WSYLA	FDIMWGQGLTVTVSS				122
H10	EVQLVESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	DYDIF	EMDYMWGQGLTVTVSS				124
H11	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	ANRDA	FDIMWGQGLTVTVSS				126
H12	EVQLVESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	EGNR	VTSAFDIMWGQGLTVTVSS				128
H13	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	GLGDS	SGYILWGQGLTVTVSS				130
H14	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	GLGDS	SGYILWGQGLTVTVSS				132
H15	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	GLGDS	SGYILWGQGLTVTVSS				134
H16	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	WTRDA	FDIMWGQGLTVTVSS				136
H17	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	QCALDA	FDIMWGQGLTVTVSS				138
H18	EVQLVESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	ERGS	SLDNMDYMWGQGLTVTVSS				140
H19	QVQLVESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	DSSG	FTYEMDYMWGQGLTVTVSS				142
H20	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	SSSWY	WNAFDIMWGQGLTVTVSS				144
H21	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	YRSF	GESYWGQGLTVTVSS				146
H22	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	GPR	GRGDIYFDIMWGQGLTVTVSS				148
H23	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	GLAAG	QCDIMWGQGLTVTVSS				150
H24	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	DGG	TYVYEMDYMWGQGLTVTVSS				152
H25	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	SGY	DAFDIMWGQGLTVTVSS				154
H26	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	YSY	GVGIDIMWGQGLTVTVSS				156
H27	EVQLVQSGGVPQPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	IGP	GDFDYMWGQGLTVTVSS				158
H28	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	HRSS	WAVYFDIMWGQGLTVTVSS				160
H29	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	VGS	WYVYFDIMWGQGLTVTVSS				162
H30	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	AYSS	GWYDYYEMDYMWGQGLTVTVSS				164
H31	EVQLVQSGGVPQPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	ASV	DAFDIMWGQGLTVTVSS				166
H32	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	ASV	DAFDIMWGQGLTVTVSS				168
H33	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	GLGDS	SGYILWGQGLTVTVSS				170
H34	QVQLQESGPGLVKPSGTL	SLTCAVSGGSGIS	SSNNWWSWVRQPPCKGLEWIGETIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAR	DHG	FFDYMWGQGLTVTVSS				172

H35 QVQLVQSGGGLVQPGSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVS<sup>174</sup>YTSSSSSSTYYADSVYGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRFGSGHLPDYWGQGLTVTVSS 174  
H36 QVQLVQSGGGLVQPGSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVS<sup>175</sup>YTSSSSSSTYYADSVYGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRFGSGHLPDYWGQGLTVTVSS 175  
H37 EVQLVESGGPLGVKPPSGTLSTCAVSGGSISSNNWWSWVRQPPGKGLEWIGETIYHSGSTNNYNP<sup>176</sup>SLKSRVTISVDTSKKNQFSLKLSSVTAADTAVYYCARVGYSSGRDVDYWGQGLTVTVSS 176  
H38 EVQLVESGGPLGVKPPSGTLSTCAVSGGSISSNNWWSWVRQPPGKGLEWIGETIYHSGSTNNYNP<sup>177</sup>SLKSRVTISVDTSKKNQFSLKLSSVTAADTAVYYCARDSSSWYYGMDMWGQGLTVTVSS 177  
H39 EVQLVESGGPLGVKPPSGTLSTCAVSGGSISSNNWWSWVRQPPGKGLEWIGETIYHSGSTNNYNP<sup>178</sup>SLKSRVTISVDTSKKNQFSLKLSSVTAADTAVYYCARSTWSLDYWGQGLTVTVSS 178  
H40 EVQLVESGGPLGVKPPSGTLSTCAVSGGSISSNNWWSWVRQPPGKGLEWIGETIYHSGSTNNYNP<sup>179</sup>SLKSRVTISVDTSKKNQFSLKLSSVTAADTAVYYCARLSFADPFDYWGQGLTVTVSS 179  
H41 EVQLVQSGGGLVQPGSLRLSCAASGFTFSYAMHWVRQAPGKGLEWVS<sup>180</sup>YTSSSSSSTYYADSVYGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREEVMLQAFDIWGQGLTVTVSS 180  
H42 QLQLQESGPGGLVKKPSETLSLTCTVSGGSISSNNWWSWVRQPPGKGLEWIGETIYHSGSTNNYNP<sup>181</sup>SLKSRVTISVDTSKKNQFSLKLSSVTAADTAVYYCARDRGYMDWKGGLTVTVSS 181  
H43 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>182</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARDHRFDYAWYFDLWGRGGLTVTVSS 182  
H44 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>183</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARDLTGSLDYWGQGLTVTVSS 183  
H45 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>184</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 184  
H46 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>185</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 185  
H47 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>186</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 186  
H48 EVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>187</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 187  
H49 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>188</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 188  
H50 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>189</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 189  
H51 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>190</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 190  
H52 QVQLVQSGGGLVQPGSLRLSCAASGFTFSYALISWVRQAPGQGLEWVGRIPI<sup>191</sup>LGTANYAQKFGQGRVITADKSTAYMELSSLRSEDTAVYYCARIRYDAFDYWGQGLTVTVSS 191

Light Chain

L2, L3, L4, L5,  
L6, L7, L8, L9,  
L10, L13, L14,  
L15, L16, L17,  
L19, L20, L23,  
L24, L25, L29,  
L30, L32, L33,  
L34, L37, L39,  
L42, L44, L45,  
L46, L48

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**Figure 5**

<u>Light Chain</u>	<u>CDR2 Sequence</u>
L1, L2, L3, L4, L5, L6, L7, L8, L9, L10, L11, L13, L14, L16, L17, L19, L20, L23, L24, L25, L26, L29, L30, L32, L34, L38, L39, L42, L44, L46, L48 L15, L21 L33 L37 L45, L52 L47	L G S N R A S L G S Y R A S L V S N R A S L G S N R D S L G S T R A S L G F N R A S
CONSENSUS	L G S N R A S
L27, L31 L18 L41	A A S T L Q S A A S G L Q S A T S T L E S
CONSENSUS	A A S T L Q S
L12, L36, L49 L35, L51 L28 L22	E D N Q R P S E D N R R P S Q D N K R P S G K N N R P S
CONSENSUS	E D N X R P S
L40 L43 L50	D A S R R A T D A S N R A T G A G Y R A T

**Figure 6**

<u>Light Chain</u>	<u>CDR3 Sequence</u>
L3, L5, L6, L7, L8	
L13, L14, L17, L23,	
L29, L32, L34, L38,	
L39, L42, L44, L46	M Q A L Q T P L T
L52	M Q A F Q T P L T
L1, L2, L11, L15, L25	M Q A L Q T P I T
L19, L45	M Q A L Q T P Y T
L9, L20	M Q A L Q T P F T
L4	M Q A L Q T P H T
L24	M Q A L Q T P N T
L10	M Q A L Q T P L A
L47	M Q G L Q T P L T
L26	M Q A L E M P L T
L30	M E A L Q T P F T
L33	M Q T L Q T P L S
L16	M Q G T H W P L T
L21	M Q S L E V P F T
L48	M Q A T H W P Y T
L37	M Q G T H W P Y T
CONSENSUS	M Q A L Q T P * T
*** = nonpolar side chain amino acid	
L40	Q Q R N N W P L T
L43	Q Q R S N W P L T
L41	Q Q S N S V P L T
L27	Q Q L N S Y P L T
L31	Q Q S H S P P Y T
L18	Q Q A S S F P I T
CONSENSUS	Q Q R N S * P L T
S S N	
*** = nonpolar side chain amino acid	
L12	Q S Y D S S N Q R V
L51	Q S Y D P Y N R V
L36	Q S Y D S S N V - V
L35	Q S Y Q S D N W - V
L49	Q S Y D S A N V I
	Q S Y D S S N X V
L28	Q A W D S G T V
L50	Q H Y G S S L R T
L22	N S R D I T G V H R

**Figure 7**

<u>Heavy Chain</u>	<u>CDR1 Sequence</u>					
H1, H2, H3, H5, H6, H7, H8, H9, H10, H11, H13, H14, H15, H16, H17, H19, H20, H23, H25, H26, H29, H30, H32, H33, H34, H37, H38, H39, H44, H46, H47, H52 H42, H45 H21	S	S	N	W	W	S
	-	S	N	W	W	S
	S	N	I	W	W	S
CONSENSUS	S	S	N	W	W	S
H4, H36, H49 H50 H28 H22	G	Y	Y	W	S	
	N	Y	D	W	S	
	N	Y	Y	W	S	
	D	F	Y	W	S	
CONSENSUS	X	Y	Y	W	S	
H12, H18 H40, H43, H51 H31, H35 H41, H48	S	Y	A	M	S	
	S	Y	A	I	S	
	S	Y	G	M	H	
	S	Y	A	M	H	
CONSENSUS	S	Y	A	M	S	H
H27	S	H	G	M	H	
H24	S	S	S	Y	Y	W G

**Figure 8**

<u>Heavy Chain</u>	<u>CDR2 Sequence</u>																
H1, H2, H3, H5, H6, H7, H10, H11, H13, H14, H15, H16, H17, H19, H20, H23, H25, H26, H29, H30, H32, H33, H34, H37, H38, H39, H42, H44, H45, H46, H47, H52	E	I	Y	H	S	G	S	T	N	Y	N	P	S	L	K	S	
H8	E	I	Y	H	S	G	S	T	N	Y	N	P	S	L	E	S	
H36, H49	E	I	N	H	S	G	S	T	N	Y	N	P	S	L	K	S	
H21	E	V	Y	H	S	G	S	T	N	Y	N	P	S	L	K	S	
H4	E	I	N	H	S	G	S	T	N	Y	N	R	S	L	K	S	
H9	Y	I	Y	Y	S	G	S	T	Y	Y	N	P	S	L	K	S	
H50	T	I	Y	S	S	G	S	T	Y	Y	S	P	S	L	K	S	
H24	S	I	Y	Y	S	G	S	T	Y	Y	N	P	S	L	K	S	
H28	Y	I	S	D	S	G	N	T	N	Y	N	P	S	L	K	S	
H22	E	V	N	P	R	G	S	T	N	Y	N	P	S	L	K	S	
CONSENSUS	E	I	Y	H	S	G	S	T	N	Y	N	P	S	L	K	S	
	Y	V	N	Y					Y								
H18	T	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
H12	A	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
H41	T	I	S	S	N	G	D	S	T	Y	Y	A	D	S	V	K	G
H27, H31	V	I	S	Y	D	G	S	N	K	Y	Y	A	D	S	V	K	G
H35	Y	I	S	S	S	S	S	T	I	Y	Y	A	D	S	V	K	G
CONSENSUS	X	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
			S			S											
H40, H43	R	I	I	P	I	L	G	I	A	N	Y	A	Q	K	F	Q	G
H48	W	I	N	A	G	N	G	N	T	K	Y	S	Q	K	F	Q	G
H51	I	I	N	P	S	G	G	S	T	S	Y	A	Q	K	F	Q	G



**Figure 9**

Heavy Chain	CDR3 Sequence															
H5	-	Y	S	S	S	R	N	D	A	F	D	I				
H6	-	-	-	D	G	Q	L	D	A	F	D	I				
H9	-	-	-	W	S	Y	L	D	A	F	D	I				
H11	-	-	-	A	N	R	D	D	A	F	D	I				
H13	E	G	N	R	T	V	T	S	A	F	D	I				
H16	-	-	W	T	G	R	T	D	A	F	D	I				
H17	-	-	-	Q	G	A	L	D	A	F	D	I				
H20	-	S	S	S	W	Y	W	N	A	F	D	I				
H25	-	-	-	-	S	G	Y	D	A	F	D	I				
H32	-	-	-	-	A	S	V	D	A	F	D	I				
H39	-	-	-	L	S	F	A	D	P	F	D	I				
H41	-	-	E	E	V	W	L	Q	A	F	D	I				
H45	-	-	-	-	I	R	Y	D	A	F	D	I				
H46	-	-	-	T	A	A	H	D	A	F	D	I				
H51			D	R	W	R	Y	D	A	F	D	I				
CONSENSUS	-	-	-	X	S	R	L	D	A	F	D	I				
H7			-	-	-	-	-	F	W	D	Y	Y	G	M	D	V
H52										E	K	S	G	M	D	V
H8			-	-	-	-	-	-	D	R	Y	Y	G	M	D	V
H10			-	-	-	-	-	D	Y	D	I	F	G	M	D	V
H18			-	E	R	G	S	G	W	S	L	D	N	M	D	V
H19			-	-	-	-	D	S	S	G	F	Y	G	M	D	V
H24			-	-	-	D	G	G	Y	Y	Y	Y	G	M	D	V
H48								H	S	Y	Y	Y	G	M	D	V
H30			-	-	-	V	S	G	Y	Y	Y	Y	G	M	D	V
H31			A	Y	S	S	G	W	Y	D	Y	Y	G	M	D	V
H37			-	-	-	D	S	S	S	W	Y	Y	G	M	D	V
H40			-	G	S	G	S	Y	Y	D	Y	Y	Y	M	D	V
H42			-	-	-	-	-	-	-	D	K	G	Y	M	D	V
CONSENSUS			-	-	-	-	S	X	Y	D	Y	Y	G	M	D	V
H2	-	-	-	-	G	V	E	Q	I	D	Y					
H3	-	-	N	L	A	A	G	A	V	A	Y					
H4	-	-	L	S	Y	G	S	G	V	D	Y					
H12	-	G	G	W	Y	G	D	Y	F	D	Y					
H23	-	G	I	A	A	A	G	Q	G	D	Y					
H26	-	Y	S	Y	G	T	V	G	I	D	Y					
H27	-	-	-	I	G	P	G	G	F	D	Y					
H29	-	-	V	G	S	G	W	Y	V	D	Y					
H34	-	-	-	-	D	H	G	P	F	D	Y					
H35	D	R	F	G	S	G	H	L	P	D	Y					
H36	V	G	Y	S	S	G	R	D	V	D	Y					
H38	-	-	-	-	S	T	W	S	L	D	Y					
H44	-	-	-	D	L	T	G	S	L	D	Y					
H47	-	D	S	S	G	Q	G	Y	F	D	Y					
CONSENSUS	-	-	X	X	G	G	G	X	*	D	Y					
*** = nonpolar side chain amino acids																
H22	G	P	R	P	G	R	D	G	Y	N	Y	F	D	N		
H28	-	-	-	H	R	S	S	W	A	W	Y	F	D	L		
H43	-	-	D	H	R	F	D	Y	A	W	Y	F	D	L		
CONSENSUS	-	-	X	H	R	X	D	X	A	W	Y	F	D	L		
H1	F	N	Y	Y	D	S	S	V								
H14, H15, H33	-	G	L	G	D	S	S	G	Y	I	L					
H19	-	-	-	-	D	S	S	G	F	Y	G	M	D	V		
H37	-	-	-	-	D	S	S	S	W	Y	Y	G	M	D	V	

H47	-	-	-	-	D	S	S	G	Q	G	Y	F	D	Y
CONSENSUS	-	-	-	-	D	S	S	G	X	X	X	-	-	-
H21	Y	R	S	F	G	E	S	Y						
H49	V	G	Y	S	H	G	E	E	V	L	D	V		
H50	A	R	G	Y	S	S	P	F	D	P				

Figure 10

1 MKSGSGGGSP TSLWGLLFLS AALSLWPTSG EICGPGIDIR NDYQQLKRLE NCTVIEGYLH  
 61 ILLISKAEDY RSYRFPKLTV ITEYLLLFVRV AGLES LGDLF PNLTVIRGWK LFYNYALVIF  
 121 EMTNLKDIGL YNLRNITRGA IRIEKNADLC YLSTVDWSLI LDAVSNNYIV GNKPPKECGD  
 181 LCPGTMEEKP MCEKTTINNE YNYRCWTTNR CQKMCPSTCG KRACTENNEC CHPECLGSCS  
 241 APDNDTACVA CRHYYYAGVC VPACPPNTYR FEGWRCVDRD FCANILSAES SDSEGFVIHD  
 301 GECMQECPSG FIRNGSQSMY CIPCEGPCPK VCEEEKTKTKT IDSVTSAQML QGCTIFKGNL  
 361 LINIRRGNNI ASELENFMGL IEVVTGYVKI RHSHALVSLS FLKNLRLILG EEQLEGNYSF  
 421 YVLDNQNLQQ LWDWDHRNLT IKAGKMYFAF NPKLCVSEIY RMEEVTGTEG RQSKGDINTR  
 481 NNGERASCES DVLHFTSTTT SKNRITITWH RYRPPDYRDL ISFTVYYKEA PFKNVTEYDG  
 541 QDACGSNSWN MVDVDLPPNK DVEPGILLHG LKPWTQYAVY VKAVTLTMVE NDHIRGAKSE  
 601 ILYIRTNASV PSIPLDVLSA SNSSSQLIVK WNPPSLPNGN LSYYIVRWQR QPQDGYLYRH  
 661 NYCSKDKIPI RKYADGTIDI EEVTENPKTE VCGGEKGPCC ACPKTEAEKQ AEKEEAERYK  
 721 VFENFLHNSI FVPRPERKRR DVMQVANTTM SSRSRNTTAA DTYNITDPEE LETEYPPFES  
 781 RVDNKERTVI SNLRPFTLYR IDIHSCNHEA EKLGCASNF VFARTMPAEG ADDIPGPVTW  
 841 EPRPENSIFL KWPEPENPNG LILMYEIKYG SQVEDQRECV SRQEYRKYGG AKLNRLNPGN  
 901 YTARIQATSL SGNGSWTDPV FFYVQAKTGY ENFIHLDEVD GCKPCICTVP EVSSVFIFPP  
 961 KPKDVLITITL TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH TAQTQPREEQ FNSTFRSVSE  
 1021 LPIMHQDWLN GKEFKCRVNS AAFPAPIEKT ISKTKGRPKA PQVYTIPPPK EQMAKDKVSL  
 1081 TCMITDFFPE DITVEWQWNG QPAENYKNTQ PIMDTDGSYF VYSKLVQKS NWEAGNTFTC  
 1141 SVLHEGLHNNH HTEKSLSHSP GK

Figure 11

1 MGTGGRRGAA AAPLLVAVAA LLLGAAGHLY PGEVCPGMDI RNNLTRLHEL ENCSVIEGHL  
 61 QILLMFKTRP EDFRDLSPFK LIMITDYLLL FRVYGLES�K DLFPNLTVIR GSRLFFNYAL  
 121 VIFEMVHLKE LGLYNLMNIT RGSVRIEKNN ELCYLATIDW SRILDSVEDN HIVLNKDDNE  
 181 ECGDICPGTA KGKTNCPATV INGQFVERCW THSHCQKVCP TICKSHGCTA EGLCCHSECL  
 241 GNCSQPDDPT KCVACRNFYL DGRCVETCPP PYYHFQDWRC VNFSFCQDLH HKCKNSRRQG  
 301 CHQYVIHNNK CIPECPSGYT MNSSNLLCTP CLGPCPKVCH LLEGEKTIDS V TSAQELRGC  
 361 TVINGSLIIN IRGGNNLAAE LEANGLLIEE ISGYLKIRRS YALVSLSFRR KLRLIRGETL  
 421 EIGNYSFYAL DNQNLRLWD WSKHNLTTTQ GKLFPHYNPK LCLSEIHKME EVSGTKGRQE  
 481 RNDIALKTNG DKASCENELL KFSYIRTSFD KILLRWEFYW PPDFRDLLGF MLFYKEAPYQ  
 541 NVTEFDGQDA CGSNSWTVVD IDPPLRSNDP KSQNHPGWLM RGLKPWTQYA IFVKTLVTFS  
 601 DERRTYGAKS DIIYVQTDAT NPSVPLDPIS VSNSSSQIIL KWKPPSDPNG NITHYLVFWE  
 661 RQAEDSELFE LDYCLKGLKL PSRTWSPPFE SEDSQKHNQS EYEDSAGECC SCPKTD SQIL  
 721 KELEESSFRK TFEDYLHNVV FVPRKTSSGT GAEDPRPSRK RRLG DVGNV TVAVPTVAAF  
 781 PNTSSTSVPT SPEEHRPF EK VVNKESLVIS GLRHFTGYRI ELQACNQDTP EERCSVAAYV  
 841 SARTMPEAKA DDIVGPVTHE IFENNVVHLM WQEPKEPNGL IVLYEVSYRR YGDEELHLCV  
 901 SRKHFALERG CRLRGLSPGN YSVRIRATSL AGNGSWTEPT YFYVTDYLDV PSNIAKVDGC  
 961 KPCICTVPEV SSVFIFPPKP KDVLTTITLTP KVTCVVVDIS KDDPEVQFSW FVDDVEVHTA  
 1021 QTQPREEQFN STFRSVSELP IMHQDWLNGK EFKCRVNSAA FPAPIEKTIS KTKGRPKAPO  
 1081 VYTIPPPKEQ MAKDKVSLTC MITDFFPEDI TVEWQWNGQP AENYKNTQPI MDTDGSYFVY  
 1141 SKLNVQKSNW EAGNTFTCSV LHEGLHNNHT EKSLSHSPGK

Figure 12

```

1      MKSGSGGG SPTSLWGLLF LSAALSLWPT SGEICGPGID IRNDYQQLKR
51     LENCTVIEGY LHILLISKAE DYRSYRFPKL TVITEYLLLF RVAGLES LGD
101    LFPNLTVIRG WKLFYNYALV IFEMTNLKDI GLYNLRNITR GAIRIEKNAD
151    LCYLSTVDWS LILDAVSNNY IVGNKPPKEC GDLCPGTMEE KPMCEKTTIN
201    NEYNYRCWTT NRCQKMCPST CGKRACTENN ECCHPECLGS CSAPDNDTAC
251    VACRHYYYAG VCV PACPPNT YRFEGWRCVD RDFCANILSA ESSDSEGFVI
301    HDGECMQECP SGFIRNGSQS MYCIPCEGPC PKVCEEEKKT KTIDSVTSAQ
351    MLQGCTIFKG NLLINIRRG NIASLENFM GLIEVVTGYV KIRHSHALVS
401    LSFLKNLRLI LGEEQLEGNY SFYVLDNQNL QQLWDWDHRN LTIKAGKMYF
451    AFNPKLCVSE IYRMEEVTGT KGRQSKGDIN TRNNGERASC ESDVLHFTST
501    TTSKNRIIIT WHRYRPPDYR DLISFTVYYK EAPFKNVTEY DGQDACGSNS
551    WNMVDVDLPP NKDVEPGILL HGLKPWTQYA VYVKAVTLM VENDHIRGAK
601    SEILYIRTNA SVPSIPLDVL SASNSSQLI VKWNPPSLPN GNLSYYIVRW
651    QRQPQDGYLY RHNYCSKDKI PIRKYADGTI DIEVTENPK TEVCGGEKGP
701    CCACPKTEAE KQAEKEEA EY RKVFENFLHN SIFVPRPERK RRDVMQVANT
751    TMSSRSRNTT AADTYNITDP EELETEY PFF ESRVDNKERT VISNLRPFTL
801    YRIDIHSCNH EAEKLGC SAS NFVFARTMPA EGADDIPGPV TWEPRPENSI
851    FLKWPEPENP NGLILMYEIK YGSQVEDQRE CVSRQEYRKY GGAKLNRLNP
901    GNYTARIQAT SLSGNGSWTD PVFFYVQAKT GYEAAAARKC SLTGKWTNDL
951    GSNMTIGAVN SKGEFTGTYT TAVTATSNEI KESPLHGTQN TINKRTQPTF
1001   GFTVNWK FSE STTVFTGQCF IDRNGKEVLK TMWLLRSSVN DIGDDWKATR
1101   VGINIFTRLR TQKE

```

Figure 13

**Kappa light chain constant region*****Nucleotide Sequence***

cgaactgtggctgcaccatctgtcttcattctcccgccatctgatgagcagttgaaatctggaactgcctctgttggtgcctgc  
tgaataactttatcccagagagggccaaagtacagtgggaaggtggataacgccctccaatcgggtaactcccaggagagt  
gtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaa  
acacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcctgcacaaagagcttcaacagggggagagtgt

***Amino acid sequence***

rtvaapsvfifppsdeqlksgtasvvc1lnnfypreakvqwkvdnalqsgnsqesvteqdskdstysls  
stltlskadyekhkvyacevthqglsspvtksfnrgec

**IgG1 heavy chain constant region*****Nucleotide Sequence***

gcctccaccaagggcccatcgggtcttccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggct  
gcctgggtcaaggactacttccccgaaccgggtgacggtgctgtggaactcaggcgccctgaccagcggcggtgcacaccttc  
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***Amino acid sequence***

astkgpsvfplapsskstsggtaalgclvkdyfpepvtvswnsgaltsgvhtfpavqlqssglyslssvv  
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Figure 14

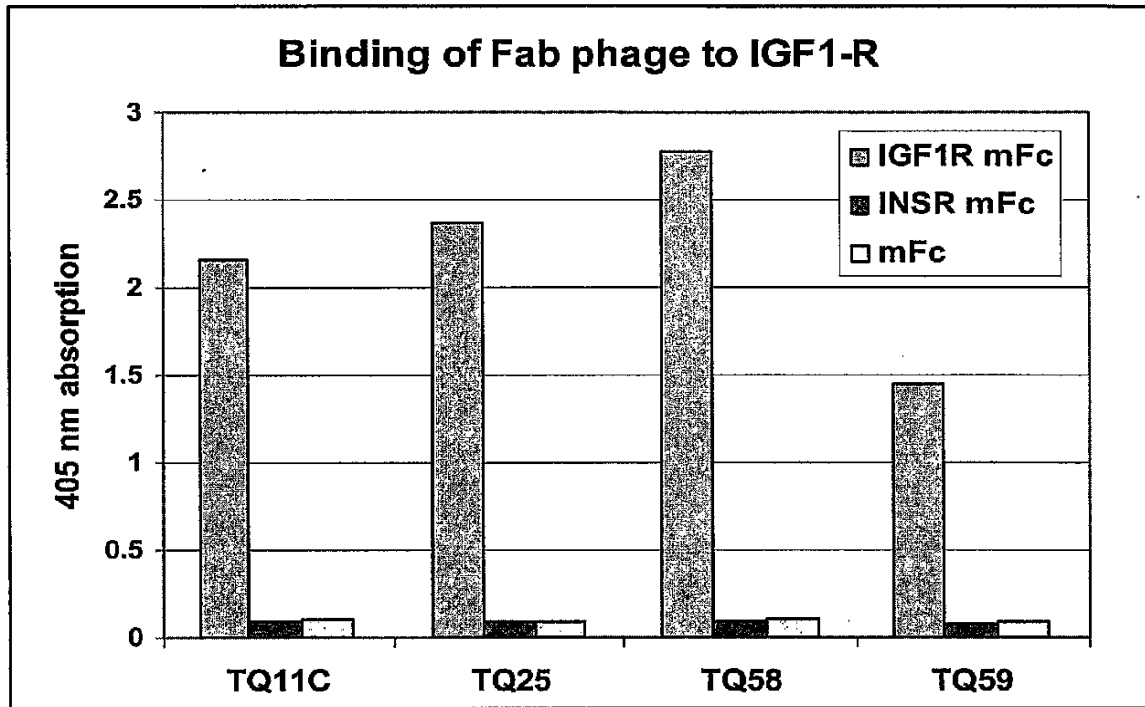
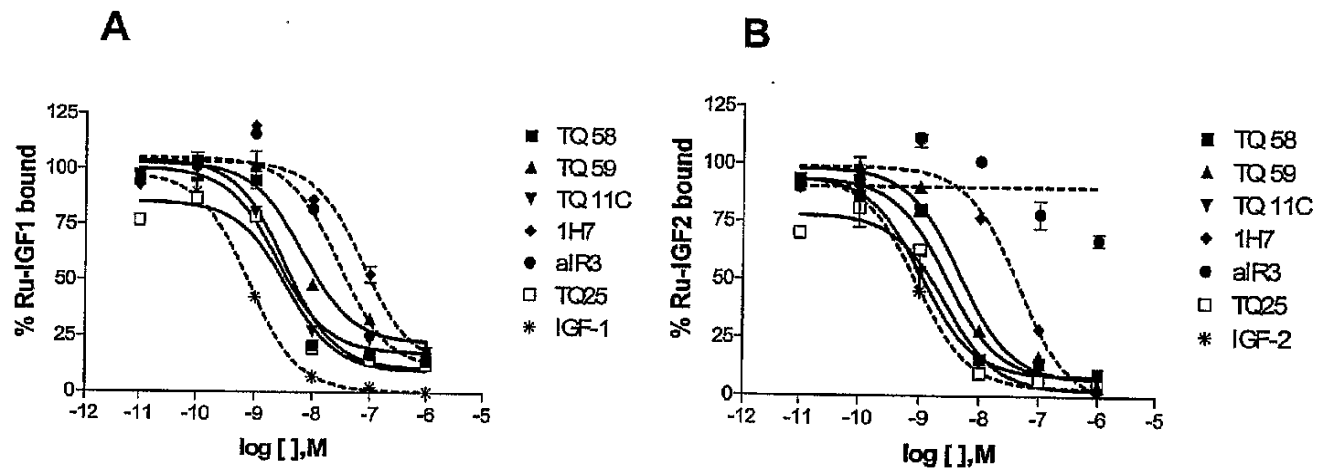
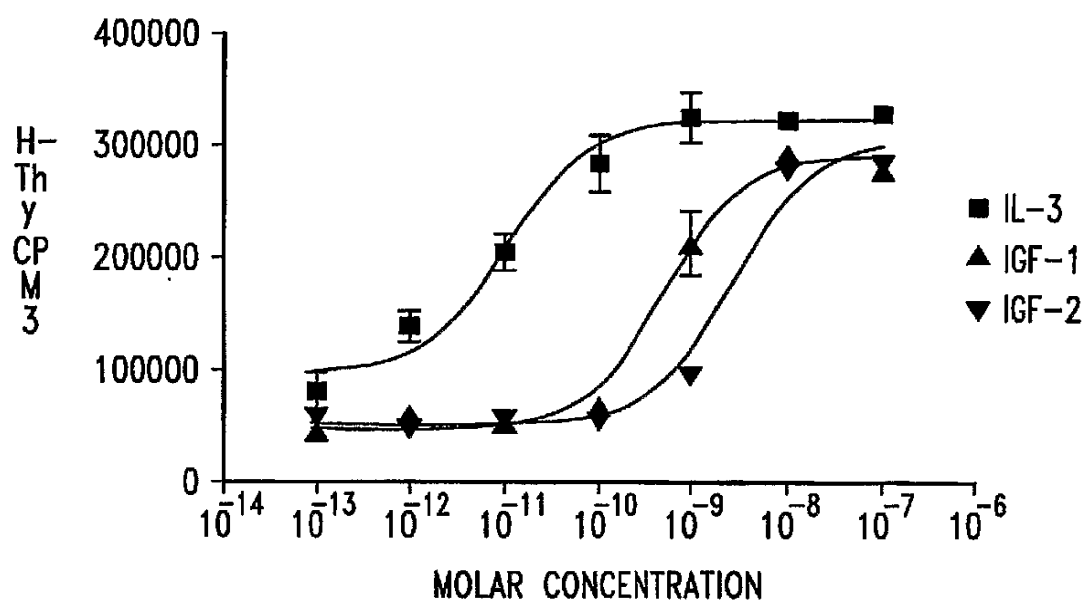
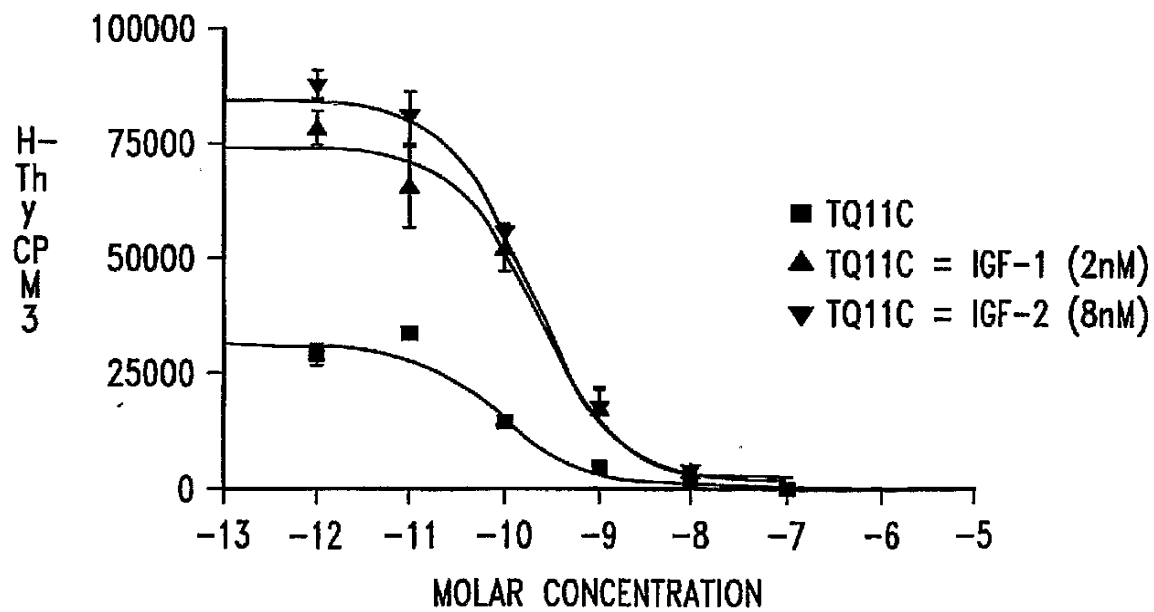


Figure 15

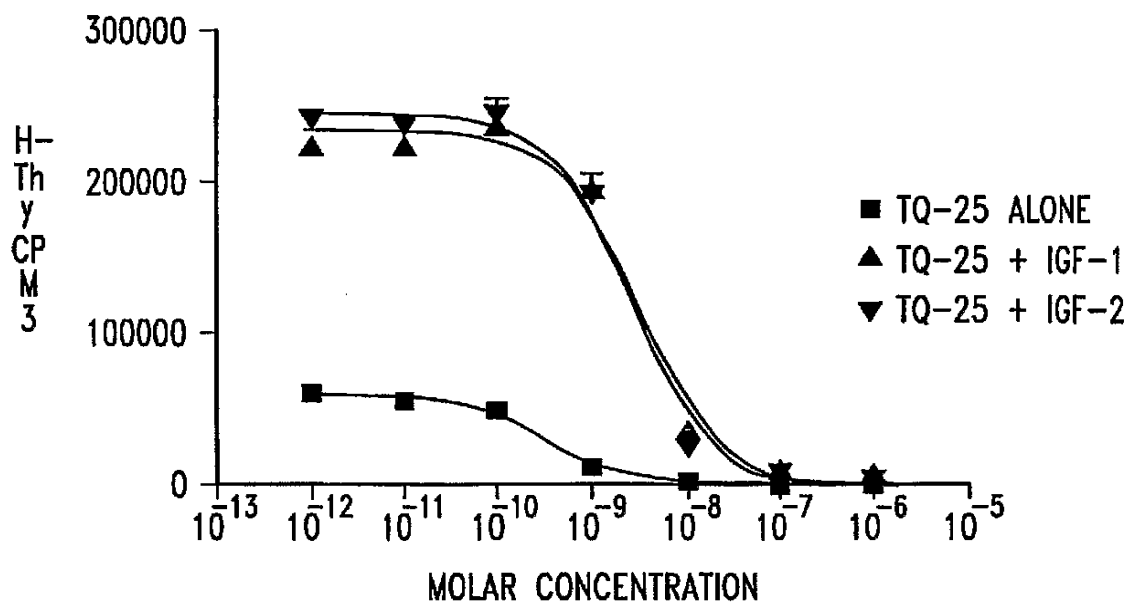
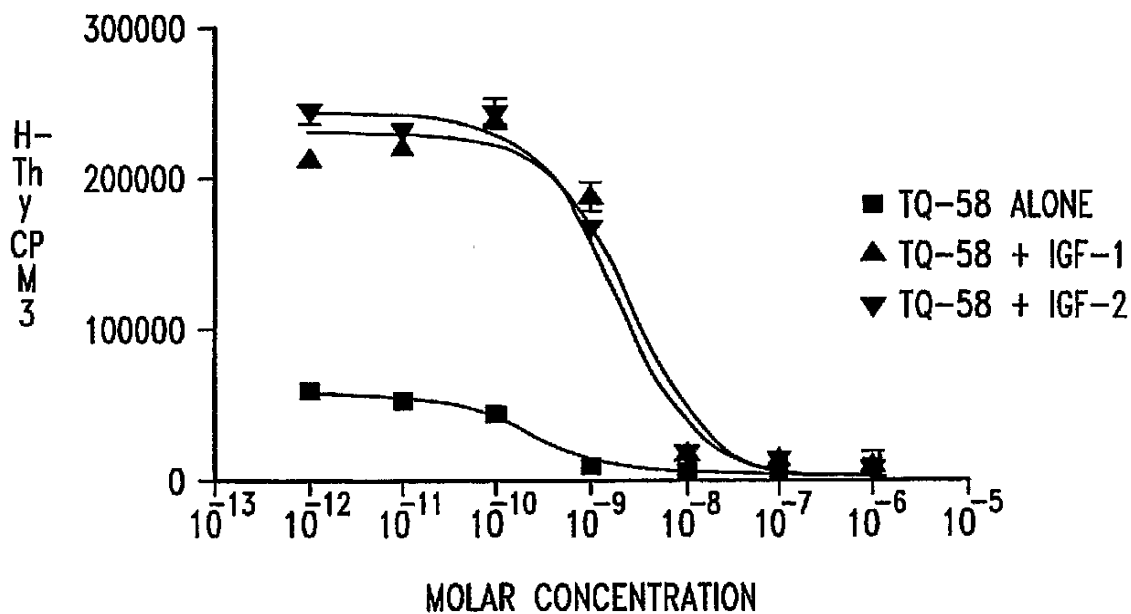




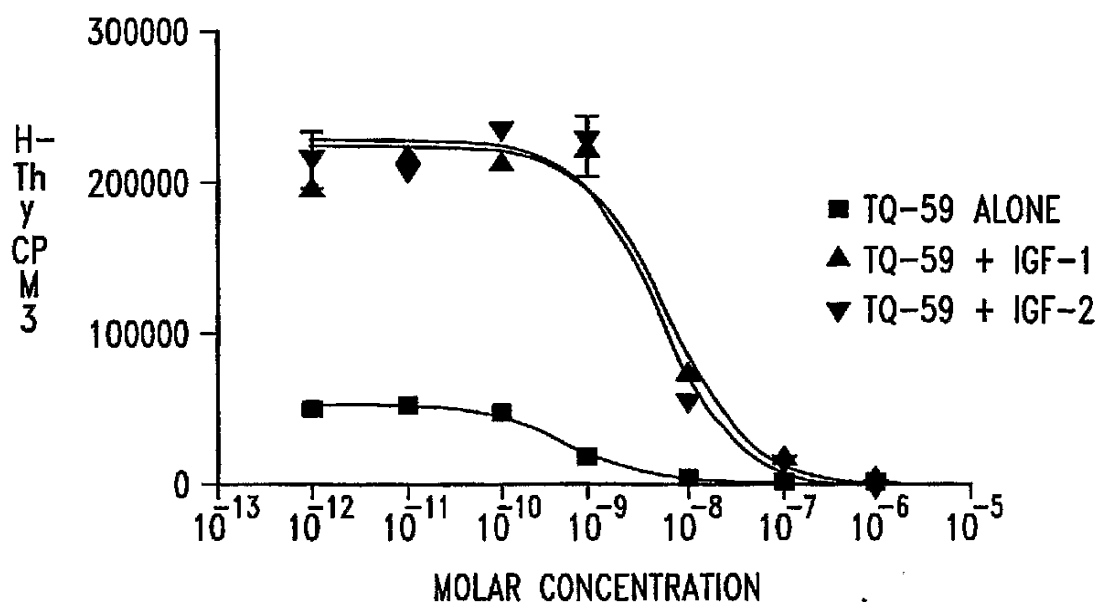
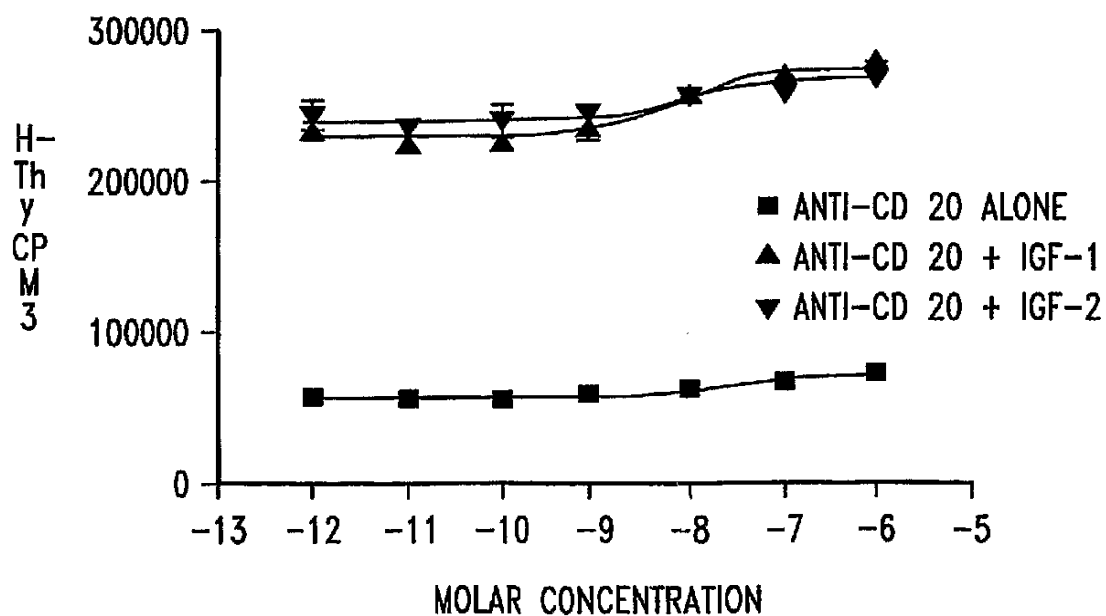
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*Fig. 16A**Fig. 16B*

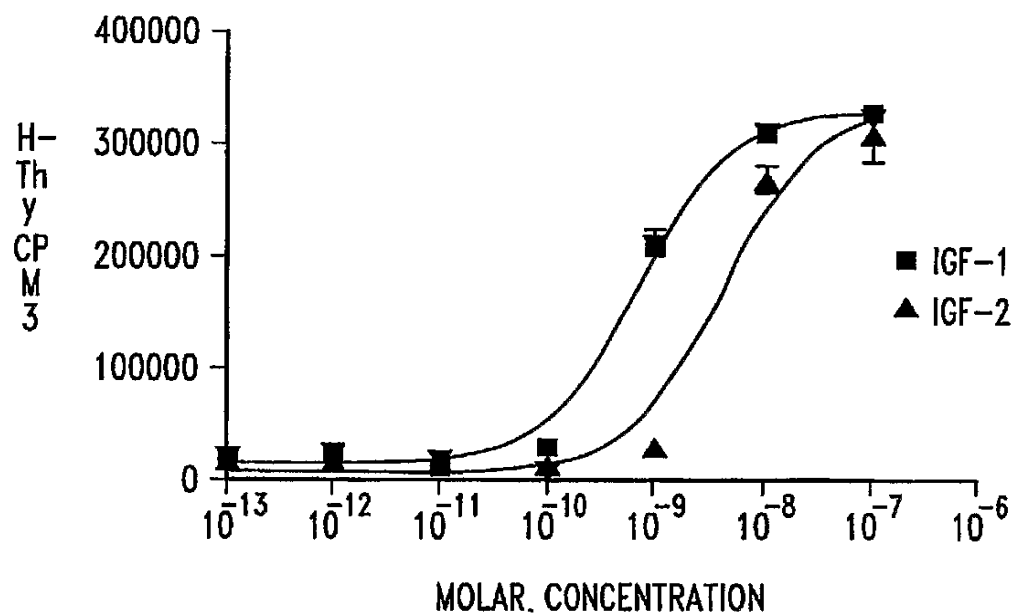
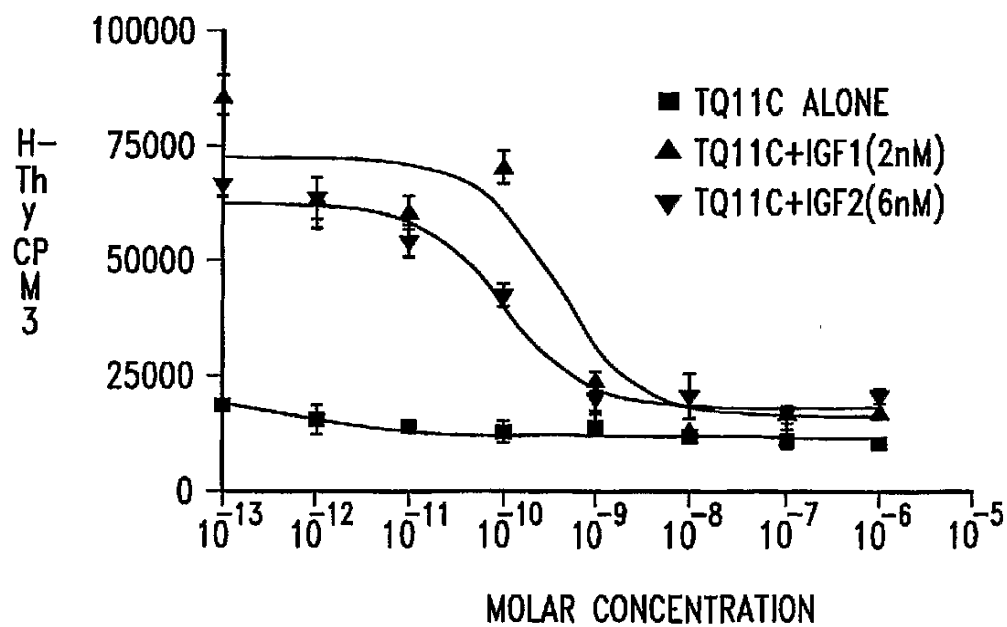
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*Fig. 16C**Fig. 16D*

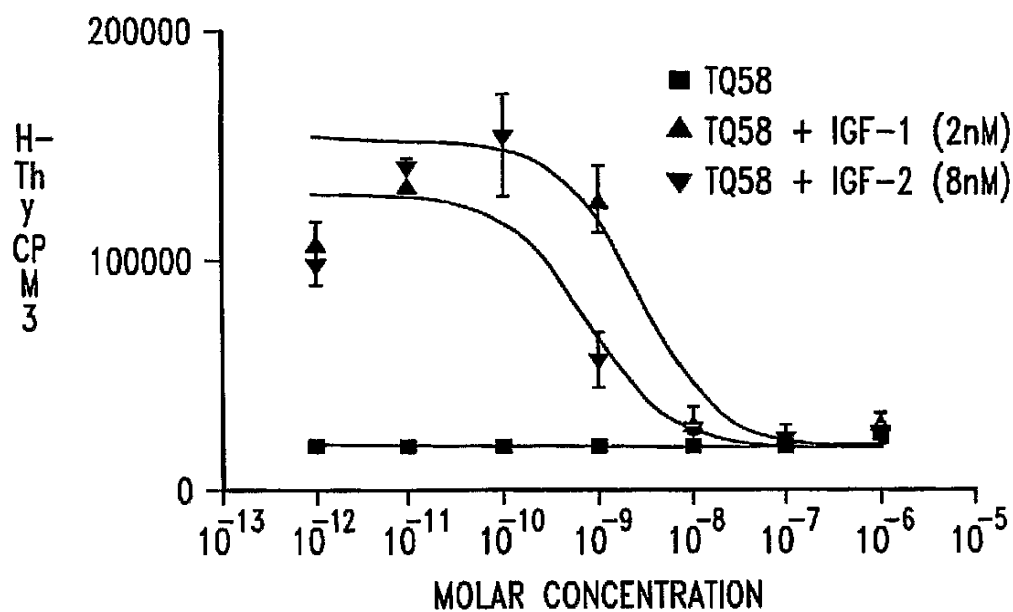
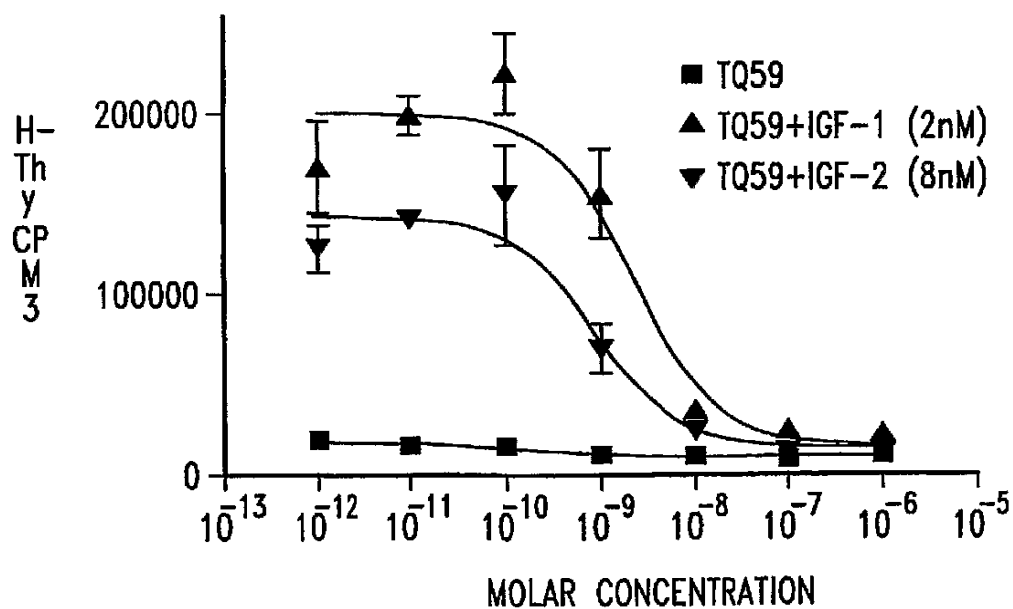
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*Fig. 16E**Fig. 16F*

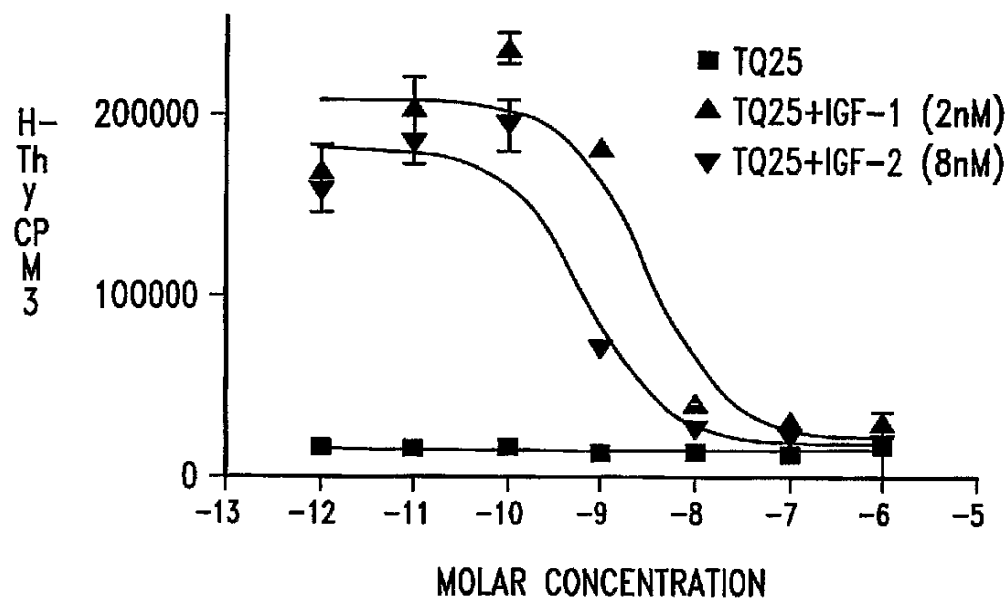
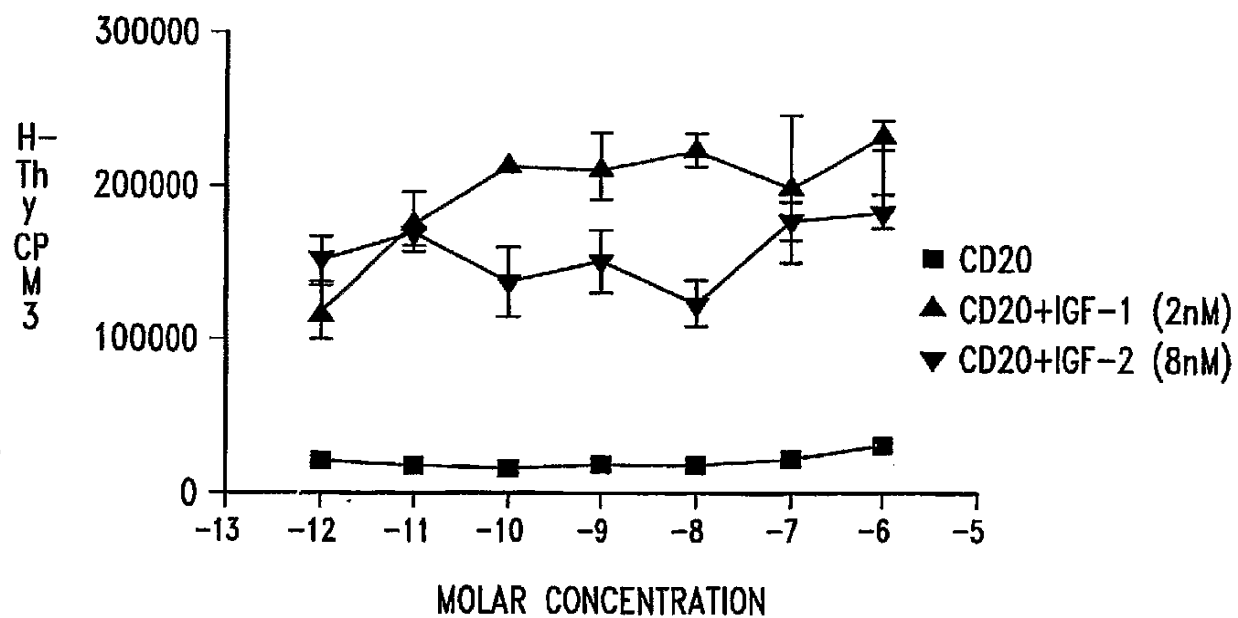
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*Fig. 17A**Fig. 17B*

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*Fig. 17C**Fig. 17D*

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*Fig. 17E**Fig. 17F*

## SEQUENCE LISTING

<110> Calzone, Frank J.  
 Deshpande, Rajendra V.  
 Tsai, Mei-Mei

<120> COMPOSITIONS AND METHODS RELATING TO ANTI IGF-1 RECEPTOR  
 ANTIBODIES

<130> A-954 (WO)

<140> --to be assigned--  
 <141> 2005-12-20

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 <151> 2004-12-22

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Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser	
20 25 30	
agt gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct	144
Ser Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct	192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro	
50 55 60	
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc	240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
65 70 75 80	
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct	288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala	
85 90 95	
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 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
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atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga gag ccg gcc	48
Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala	
1 5 10 15	
tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt aat gga tac	96
Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr	



20							25					30					
aac	tat	ttg	gat	tgg	tac	ctg	cag	aag	cca	ggg	cag	tct	cca	cag	ctc	144	
Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Gln	Leu		
		35					40					45					
ctg	atc	tat	ttg	ggt	tct	aat	cgg	gcc	tcc	ggg	gtc	cct	gac	agg	ttc	192	
Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro	Asp	Arg	Phe		
	50					55					60						
agt	ggc	agt	gga	tca	ggc	aca	gat	ttt	aca	ctg	aaa	atc	agc	aga	gtg	240	
Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	Ser	Arg	Val		
65					70					75					80		
gag	gct	gag	gat	gtt	ggg	gtt	tat	tac	tgc	atg	caa	gct	cta	caa	act	288	
Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala	Leu	Gln	Thr		
				85					90					95			
ccg	atc	acc	ttc	ggc	caa	ggg	aca	cga	ctg	gag	att	aaa				327	
Pro	Ile	Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys					
			100					105									

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<210> 4
<211> 109
<212> PRT
<213> Artificial
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<220>  
<223> Synthetic Construct

<400> 4

Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly	Glu	Pro	Ala
1				5					10					15	

Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr  
20 25 30

Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu  
35 40 45

Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe  
50 55 60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val  
65 70 75 80

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr  
85 90 95

Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105

<210> 5  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 5  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95  
 cta caa act cca ctc act ttc ggc ggc ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 6  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 6  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 7  
<211> 336  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(336)

<400> 7  
gaa att gtg atg acg cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15  
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30  
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45  
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60  
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80  
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
85 90 95  
cta caa act cct cac act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
Leu Gln Thr Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 8  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 8

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 9  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 9

gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
           35                          40                          45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
           50                          55                          60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
           65                          70                          75                          80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                           85                          90                          95

cta caa acc cct ctc act ttc ggc cct ggg acc aaa gtg gat atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
                           100                          105                          110

<210> 10  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 10

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                          5                          10                          15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
           20                          25                          30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
           35                          40                          45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
           50                          55                          60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
           65                          70                          75                          80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                           85                          90                          95

Leu Gln Thr Pro Leu Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
                           100                          105                          110

<210> 11

<211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 11  
 gat gtt gtg atg act cag tct cca ctc tcc ctg gcc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ala Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95  
 cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 12  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 12  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ala Val Thr Pro Gly  
 1 5 10 15  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser

35                                      40                                      45  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
     50                                      55                                      60  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
     65                                      70                                      75                                      80  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                                     85                                      90                                      95  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                                     100                                      105                                      110

<210> 13  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 13  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                                      5                                      10                                      15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
                                     20                                      25                                      30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
                                     35                                      40                                      45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
     50                                      55                                      60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
     65                                      70                                      75                                      80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                                     85                                      90                                      95  
 cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                                     100                                      105                                      110

<210> 14  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 14

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 15  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 15

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30



aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
           35                                  40                                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
           50                                  55                                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
           65                                  70                                  75                                  80

agc aga gtg gag gct gaa gat gtt ggg gtt tat tac tgt atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                                   85                                  90                                  95

cta caa acc ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                                   100                                  105                                  110

<210> 16  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 16

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                                  5                                  10                                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
           20                                  25                                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
           35                                  40                                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
           50                                  55                                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65                                  70                                  75                                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                                   85                                  90                                  95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
           100                                  105                                  110

<210> 17  
 <211> 336

<212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 17  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95  
 cta caa act ccg ttc acc ttc ggc caa ggg aca cga ctg gag att aaa 336  
 Leu Gln Thr Pro Phe Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
 100 105 110

<210> 18  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 18  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Phe Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
 100 105 110

<210> 19  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 19  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95  
 cta caa act cct ctg gcg ttc ggc caa ggg acc aag gtg gaa atc aaa 336  
 Leu Gln Thr Pro Leu Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 20  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 20

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 21  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 21

gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg aat tgg tac ctg cag aag cca ggg cag tct 144

```

Asn Gly Tyr Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser
   35                               40                               45

cca cag ctg ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct      192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
   50                               55                               60

gac agg ttc agt gcc agt gga tca ggc aca gat ttt aca ctg aaa atc      240
Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
   65                               70                               75                               80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct      288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
           85                               90                               95

cta caa act cct atc acc ttc ggc caa ggg aca cga ctg gag att aaa      336
Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
           100                               105                               110

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<210>  22
<211> 112
<212>  PRT
<213> Artificial

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<220>
<223> Synthetic Construct

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<400>  22

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Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1                               5                               10                               15

```

```

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
           20                               25                               30

```

```

Asn Gly Tyr Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser
   35                               40                               45

```

```

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
   50                               55                               60

```

```

Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
   65                               70                               75                               80

```

```

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
           85                               90                               95

```

```

Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
           100                               105                               110

```

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<210>  23
<211> 333
<212>  DNA

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<213> Artificial

<220>

<223> light chain variable region

<220>

<221> CDS

<222> (1)..(333)

<400> 23

aat	ttt	atg	ctg	act	cag	ccc	cac	tct	gtg	tcg	gag	tct	ccg	ggg	aag	48
Asn	Phe	Met	Leu	Thr	Gln	Pro	His	Ser	Val	Ser	Glu	Ser	Pro	Gly	Lys	
1				5					10					15		

acg	gta	acc	atc	tcc	tgc	acc	cgc	agc	agt	ggc	agc	att	gcc	agc	aac	96
Thr	Val	Thr	Ile	Ser	Cys	Thr	Arg	Ser	Ser	Gly	Ser	Ile	Ala	Ser	Asn	
			20					25					30			

tat	gtg	cag	tgg	tac	cag	cag	cgc	ccg	ggc	agt	tcc	ccc	acc	act	gtg	144
Tyr	Val	Gln	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Ser	Ser	Pro	Thr	Thr	Val	
		35					40					45				

atc	tat	gag	gat	aac	caa	aga	ccc	tct	ggg	gtc	cct	gat	cgg	ttc	tct	192
Ile	Tyr	Glu	Asp	Asn	Gln	Arg	Pro	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser	
	50					55					60					

ggc	tcc	atc	gac	agc	tcc	tcc	aac	tct	gcc	tcc	ctc	acc	atc	tct	gga	240
Gly	Ser	Ile	Asp	Ser	Ser	Ser	Asn	Ser	Ala	Ser	Leu	Thr	Ile	Ser	Gly	
65						70				75					80	

ctg	aag	act	gag	gac	gag	gct	gac	tac	tac	tgt	cag	tct	tat	gat	agc	288
Leu	Lys	Thr	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Ser	
				85					90					95		

agc	aat	cag	aga	gtg	ttc	ggc	gga	ggg	acc	aag	ctg	acc	gtc	cta		333
Ser	Asn	Gln	Arg	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu		
			100					105					110			

<210> 24

<211> 111

<212> PRT

<213> Artificial

<220>

<223> Synthetic Construct

<400> 24

Asn	Phe	Met	Leu	Thr	Gln	Pro	His	Ser	Val	Ser	Glu	Ser	Pro	Gly	Lys
1				5					10					15	

Thr	Val	Thr	Ile	Ser	Cys	Thr	Arg	Ser	Ser	Gly	Ser	Ile	Ala	Ser	Asn
			20					25					30		

Tyr	Val	Gln	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Ser	Ser	Pro	Thr	Thr	Val
		35					40					45			

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser  
 50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly  
 65 70 75 80

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser  
 85 90 95

Ser Asn Gln Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105 110

<210> 25  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 25  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95  
 cta caa acc ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 26

<211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 26

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 27  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 27

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser



35	40	45	
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct			192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro			
50	55	60	
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc			240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile			
65	70	75	80
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct			288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala			
85	90	95	
cta caa act cct ctt act ttc ggc gga ggg acc aag gtg gag atc aaa			336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Thr Lys Val Glu Ile Lys			
100	105	110	

<210> 28  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 28

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 29  
 <211> 336  
 <212> DNA  
 <213> Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 29

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga	48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly	
1 5 10 15	

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt	96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser	
20 25 30	

aat gga tac aac tat ttg gat tgg tac ctg caa aag cca ggg cag tct	144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	

cca cag ctc ctg atc tat ttg ggt tct tat cgg gcc tcc ggg gtc cct	192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro	
50 55 60	

gac agg ttc agt gcc agt gga tca ggc aca gat ttt aca ctg aaa atc	240
Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
65 70 75 80	

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct	288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala	
85 90 95	

cta caa act ccg atc acc ttc ggc caa ggg aca cga ctg gag att aaa	336
Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys	
100 105 110	

&lt;210&gt; 30

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 30

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
 100 105 110

<210> 31  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 31  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc agg gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa ggt 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
 85 90 95  
 aca cac tgg cct ctg acg ttc ggc caa ggg acc aag gtg gag atc aaa 336  
 Thr His Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 32  
 <211> 112

<212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 32

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
 85 90 95

Thr His Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 33  
 <211> 335  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(333)

<400> 33

gaa att gtg atg acg cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aa 335  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Thr Lys Val Glu Ile  
 100 105 110

<210> 34  
 <211> 111  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 34

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile  
 100 105 110

<210> 35  
 <211> 321  
 <212> DNA  
 <213> Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(321)

&lt;400&gt; 35

gac atc cag ttg acc cag tct cca tct tcc gtg tct gcg tct gtc gga	48
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly	
1 5 10 15	

gac aga gtc acc atc act tgt cgg gcg agt cag ggt att agc agg tgg	96
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp	
20 25 30	

tta gcc tgg tat caa cag aaa cca ggg aaa gcc cct aga ctc ctg atc	144
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile	
35 40 45	

tat gct gcg tcc ggt tta caa agt ggg gtc cca tca agg ttc agc ggc	192
Tyr Ala Ala Ser Gly Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly	
50 55 60	

agt gga tct ggg aca gat ttc act ctc acc atc agc aac ctg cag cct	240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro	
65 70 75 80	

gaa gat ttt gca act tac tat tgt caa cag gct agc agt ttt cca atc	288
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Ser Ser Phe Pro Ile	
85 90 95	

acc ttc ggc caa ggg aca cga ctg gag act aaa	321
Thr Phe Gly Gln Gly Thr Arg Leu Glu Thr Lys	
100 105	

&lt;210&gt; 36

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 36

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Gly Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
-----------------------------------------------------------------

50                                      55                                      60  
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro  
 65                                      70                                      75                                      80  
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Ser Ser Phe Pro Ile  
                                     85                                      90                                      95  
 Thr Phe Gly Gln Gly Thr Arg Leu Glu Thr Lys  
                                     100                                      105

<210> 37  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 37  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                                      5                                      10                                      15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
                                     20                                      25                                      30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
                                     35                                      40                                      45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
                                     50                                      55                                      60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65                                      70                                      75                                      80  
 agc aga gtg gag gct gag gat gtt gga gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                                     85                                      90                                      95  
 cta caa act ccg tac act ttt ggc cag ggg acc aag ctg gag atc aaa 336  
 Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
                                     100                                      105                                      110

<210> 38  
 <211> 112  
 <212> PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 38

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 100 105 110

&lt;210&gt; 39

&lt;211&gt; 336

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 39

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45



cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

aac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

cta caa act cca ttc act ttc ggc cct ggg acc aaa gtg gat atc aaa 336  
 Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
 100 105 110

<210> 40  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 40

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
 100 105 110

<210> 41  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>

<223> light chain variable region

<220>

<221> CDS

<222> (1)..(336)

<400> 41

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga	48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly	
1 5 10 15	

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt	96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser	
20 25 30	

cat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct	144
His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	

cca caa ctt ctg atc tat ttg ggt tct tat cgg gcc tcc ggg gtc cct	192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro	
50 55 60	

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc	240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
65 70 75 80	

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa tct	288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser	
85 90 95	

cta gaa gtt ccg ttc act ttt ggc cag ggg acc aag ctg gag atc aaa	336
Leu Glu Val Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys	
100 105 110	

<210> 42

<211> 112

<212> PRT

<213> Artificial

<220>

<223> Synthetic Construct

<400> 42

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser  
85 90 95

Leu Glu Val Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
100 105 110

<210> 43  
<211> 321  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(321)

<400> 43  
tct tct gag ctg act cag gac cct gct gtg tct gtg gcc ttg gga cag 48  
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln  
1 5 10 15  
aca gtc agg atc aca tgc caa gga gac agc ctc aga att tat tat aca 96  
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ile Tyr Tyr Thr  
20 25 30  
ggc tgg tac caa cag aag cca gga cag gcc cct gtg ctt gtc ctc ttt 144  
Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Leu Phe  
35 40 45  
ggt aag aac aat cgg ccc tca ggg atc cca gac cga ttc tct ggc tcc 192  
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser  
50 55 60  
cac tca ggg aac aca gct tcc ttg acc atc act ggg gct caa gcg gaa 240  
His Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu  
65 70 75 80  
gat gag gct gac tat tac tgt aac tcc cgg gac atc act ggt gtc cat 288  
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ile Thr Gly Val His  
85 90 95  
cga ttc ggc gga ggg acc aag ctg acc gtc cta 321  
Arg Phe Gly Gly Thr Lys Leu Thr Val Leu  
100 105

<210> 44  
<211> 107  
<212> PRT  
<213> Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 44

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln  
 1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ile Tyr Tyr Thr  
 20 25 30

Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Leu Phe  
 35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser  
 50 55 60

His Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu  
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ile Thr Gly Val His  
 85 90 95

Arg Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105

&lt;210&gt; 45

&lt;211&gt; 336

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 45

gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 46  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 46

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 47  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 47

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga	48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly	
1 5 10 15	

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt	96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser	
20 25 30	

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct	144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct	192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro	
50 55 60	

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc	240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
65 70 75 80	

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct	288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala	
85 90 95	

cta caa act cct aac act ttc ggc gga ggg acc aag gtg gag atc aaa	336
Leu Gln Thr Pro Asn Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys	
100 105 110	

&lt;210&gt; 48

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 48

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
85 90 95

Leu Gln Thr Pro Asn Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 49  
<211> 336  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(336)

<400> 49  
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15  
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30  
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45  
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60  
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80  
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
85 90 95  
cta caa act cca atc act ttc ggc cct ggg acc aaa gtg gat atc aaa 336  
Leu Gln Thr Pro Ile Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
100 105 110

<210> 50  
<211> 112  
<212> PRT  
<213> Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 50

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Ile Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
 100 105 110

&lt;210&gt; 51

&lt;211&gt; 336

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 51

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac acc tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

cca caa ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro



50	55	60	
gac agg ttc agc ggc agt gga tca ggc aca gat ttt aca ctg aaa atc			240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile			
65	70	75	80
agc aga gtg gag cct gag gat gtt ggg gtc tat tac tgc atg caa gct			288
Ser Arg Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala			
	85	90	95
cta gaa atg ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa			336
Leu Glu Met Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys			
	100	105	110

<210> 52  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 52

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Glu Met Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 53  
 <211> 321  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(321)

&lt;400&gt; 53

gac atc cag ttg acc cag tct cca tcc ttc ctg tct gca tct gta gga 48  
 Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly  
 1 5 10 15

gac aga gtc acc atc act tgc cgg gcc agt cag ggc att agc agt tat 96  
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr  
 20 25 30

tta gcc tgg tat cag caa aaa cca ggg aaa gcc cct aag ctc ctg atc 144  
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile  
 35 40 45

tat gct gca tcc act ttg caa agt ggg gtc cca tca agg ttc agc ggc 192  
 Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

agt gga tct ggg aca gaa ttc act ctc aca atc agc agc ctg cag cct 240  
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

gaa gat ttt gca act tat tac tgt caa cag ctt aat agt tac ccc ctc 288  
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu  
 85 90 95

act ttc ggc gga ggg acc aag gtg gag atc aaa 321  
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

&lt;210&gt; 54

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 54

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr  
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile  
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu  
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105

<210> 55  
<211> 315  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(315)

<400> 55  
tcc tat gtg ctg act cag cca ccc tca gtg tcc gtg tcc cca gga cag 48  
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
1 5 10 15  
  
aca gcc agc atc acc tgc tct gga gat aaa ttg ggg gat aaa tat gtt 96  
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val  
20 25 30  
  
ggc tgg tat cag caa aag gca ggc caa gcc cct gtt ttg gtc atc tat 144  
Gly Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Val Leu Val Ile Tyr  
35 40 45  
  
caa gac aac aag cga ccc tca ggg atc cct gag cga ttc tct ggc tcc 192  
Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
50 55 60  
  
aac tct ggg aac aca gcc agt ctg acc atc agc ggg acc cag gct atg 240  
Asn Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Thr Gln Ala Met  
65 70 75 80  
  
gat gag gct gac tat tac tgt cag gcg tgg gac agc ggc acg gtg ttc 288  
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Gly Thr Val Phe  
85 90 95  
  
ggc gga ggg acc aag ctg acc gtc cta 315  
Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105

<210> 56  
<211> 105  
<212> PRT  
<213> Artificial

<220>

&lt;223&gt; Synthetic Construct

&lt;400&gt; 56

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
 1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val  
 20 25 30

Gly Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Val Leu Val Ile Tyr  
 35 40 45

Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
 50 55 60

Asn Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Thr Gln Ala Met  
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Gly Thr Val Phe  
 85 90 95

Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105

&lt;210&gt; 57

&lt;211&gt; 336

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 57

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

cta caa acc ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 58  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 58

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 59  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 59

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga	48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly	
1 5 10 15	

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt	96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser	
20 25 30	

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct	144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct	192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro	
50 55 60	

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc	240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
65 70 75 80	

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg gaa gct	288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Glu Ala	
85 90 95	

cta caa act cca ttc act ttc ggc cct ggg acc aag gtg gaa atc aaa	336
Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys	
100 105 110	

&lt;210&gt; 60

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 60

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
-----------------------------------------------------------------

65				70				75				80			
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Glu	Ala
				85				90						95	
Leu	Gln	Thr	Pro	Phe	Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Glu	Ile	Lys
			100					105					110		

<210>	61
<211>	321
<212>	DNA
<213>	Artificial

<220>  
<223> light chain variable region

$\langle 220 \rangle$   
 $\langle 221 \rangle$  CDS  
 $\langle 222 \rangle$  (1) .. (321)

<400>	61																
gac atc cag ttg acc cag tct cca tcc tcc ctg tct gcg tct gtg gga																	48
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly																	
1				5					10					15			
gac aga gtc acc atc act tgc cgg tca agt caa gcc att ggt tac ttc																	96
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Gly Ile Gly Tyr Phe																	
			20					25					30				
tta aat tgg tat cag cag gaa cca ggg aaa gcc cca aag atc ctg atc																	144
Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Ile Leu Ile																	
		35					40					45					
tct gct gca tcc act ttg caa agt ggg gtc cca tca agg ttc agt ggc																	192
Ser Ala Ala Ser Thr Leu Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly																	
	50					55					60						
agt gga tct ggg aca gat ttc aca ctc tcc atc aac aat ctg caa ccc																	240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Asn Leu Gln Pro																	
65					70				75					80			
gca gat ttt gcg aca tac tac tgt caa cag agt cac agt ccc ccg tac																	288
Ala Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Pro Pro Tyr																	
				85				90						95			
act ttc ggc cag ggg acc aag gtg gag atc aaa																	321
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys																	
			100					105									

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<210> 62
<211> 107
<212> PRT
<213> Artificial
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<220>  
<223> Synthetic Construct

&lt;400&gt; 62

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Gly Ile Gly Tyr Phe  
 20 25 30

Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Ile Leu Ile  
 35 40 45

Ser Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Asn Leu Gln Pro  
 65 70 75 80

Ala Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Pro Pro Tyr  
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105

&lt;210&gt; 63

&lt;211&gt; 336

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 63

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60



gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 64  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 64

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 65  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>

&lt;221&gt; CDS

&lt;222&gt; (1)..(336)

&lt;400&gt; 65

gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga	48
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly	
1 5 10 15	

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt	96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser	
20 25 30	

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct	144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	

cca cag ctc ctg atg tat ttg gtt tct aat cgg gcc tcc ggg gtc cct	192
Pro Gln Leu Leu Met Tyr Leu Val Ser Asn Arg Ala Ser Gly Val Pro	
50 55 60	

gag agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc	240
Glu Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
65 70 75 80	

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa act	288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr	
85 90 95	

cta caa act cct ctc agt ttt ggc cag ggg acc aag ctg gag atc aaa	336
Leu Gln Thr Pro Leu Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys	
100 105 110	

&lt;210&gt; 66

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 66

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Met Tyr Leu Val Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Glu Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr  
85 90 95

Leu Gln Thr Pro Leu Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
100 105 110

<210> 67  
<211> 336  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(336)

<400> 67  
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15  
  
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30  
  
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45  
  
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60  
  
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80  
  
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
85 90 95  
  
cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 68  
<211> 112  
<212> PRT  
<213> Artificial

<220>  
<223> Synthetic Construct

&lt;400&gt; 68

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

&lt;210&gt; 69

&lt;211&gt; 330

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; light chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(330)

&lt;400&gt; 69

aat ttt atg ctg act cag ccc cac tct gtg tcg gcg tct ccg ggg aag 48  
 Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Ala Ser Pro Gly Lys  
 1 5 10 15

acg gtt acc atc tcc tgc acc cgc agc agt ggc gac att gac aac aac 96  
 Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Asp Ile Asp Asn Asn  
 20 25 30

tat gtg cag tgg tac cag cag cgc ccg ggc aat tcc ccc acc aat gtg 144  
 Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Asn Ser Pro Thr Asn Val  
 35 40 45

att tat gag gat aac cga aga ccc tct ggg gtc ccg gat cgc ttc tct 192  
 Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser  
 50 55 60

ggc tcc atc gac agc tcc tcc aac tct gcc tcc ctc acc atc tct gga 240

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly  
 65 70 75 80  
 ctg cag cct gag gac gag gct gac tac tat tgt cag tct tat caa agc 288  
 Leu Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Gln Ser  
 85 90 95

gac aat tgg gtg ttc ggc gga ggg acc aag gtg acc gtc cta 330  
 Asp Asn Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu  
 100 105 110

<210> 70  
 <211> 110  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 70

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Ala Ser Pro Gly Lys  
 1 5 10 15

Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Asp Ile Asp Asn Asn  
 20 25 30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Asn Ser Pro Thr Asn Val  
 35 40 45

Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser  
 50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly  
 65 70 75 80

Leu Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Gln Ser  
 85 90 95

Asp Asn Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu  
 100 105 110

<210> 71  
 <211> 330  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS

&lt;222&gt; (1)..(330)

&lt;400&gt; 71

```

aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag      48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1           5           10           15

```

```

acg gta acc atc tcc tgc acc cgc agc agt ggc agc att gcc agc aac      96
Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
           20           25           30

```

```

tat gtg cag tgg tac cag cag cgc ccg ggc agt tcc ccc acc act gtg      144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
           35           40           45

```

```

atc tat gag gat aac caa aga ccc tct ggg gtc cct gat cga ttc tct      192
Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
           50           55           60

```

```

ggc tcc atc gac agc tcc tcc aac tct gcc tcc ctc acc atc tct gga      240
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
           65           70           75           80

```

```

ctg aag act gag gac gag gct gac tac tac tgt cag tct tat gat agc      288
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
           85           90           95

```

```

agc aat gtg gtg ttc ggc gga ggg acc aag ctg acc gtc cta      330
Ser Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
           100           105           110

```

&lt;210&gt; 72

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 72

```

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1           5           10           15

```

```

Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
           20           25           30

```

```

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
           35           40           45

```

```

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
           50           55           60

```

```

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
           65           70           75           80

```

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser  
85 90 95

Ser	Asn	Val	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu
			100					105					110

<210>	73
<211>	336
<212>	DNA
<213>	Artificial

<220>  
<223> light chain variable region

```
<220>
<221> CDS
<222> (1) .. (336)
```

```

<400> 73
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct ggg      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1          5          10         15

```

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45

cca cag ctc ctg atc tat ttg ggt tct aac cgg gac tct ggg gtc cca 192  
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Asp Ser Gly Val Pro  
50 55 60

gac aga ttc agc ggc agt ggg tca ggc act gat ttc aca ctg aaa atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80

agc agg gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa ggt      288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
                85                         90                         95

aca cac tgg ccg tac act ttt ggc cag ggg acc agg ctg gag atc aaa 336  
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105 110

```
<210> 74
<211> 112
<212> PRT
<213> Artificial
```

<220>  
<223> Synthetic Construct

<400> 74

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Asp Ser Gly Val Pro  
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
85 90 95

Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105 110

<210> 75

<211> 336

<212> DNA

<213> Artificial

<220>

<223> light chain variable region

<220>

<221> CDS

<222> (1)..(336)

<400> 75

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15

gag tcg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
Glu Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

aat gga tac aac ttt ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
Asn Gly Tyr Asn Phe Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile



65		70		75		80	
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct							288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala							
	85			90		95	

cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aaa							336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys							
	100			105		110	

<210> 76  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 76

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly							
1		5			10		15

Glu Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser							
	20			25			30

Asn Gly Tyr Asn Phe Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser							
	35			40			45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro							
	50			55			60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile							
65			70			75	80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala							
	85				90		95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys							
	100				105		110

<210> 77  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 77  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

cta caa acc ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 78  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 78  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                     85                                    90                                    95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                     100                                    105                                    110

<210> 79  
 <211> 321  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(321)

<400> 79  
 gaa acg aca ctc acg cag tct cca gcc acc ctg tct ttg tct cca ggg 48  
 Glu Thr Thr Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
 1                    5                                    10                                    15

caa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtc tac aac tac 96  
 Gln Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Asn Tyr  
                     20                                    25                                    30

tta gcc tgg tac caa cag aag cct ggc cag gct ccc agg ctc ctc atc 144  
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
                     35                                    40                                    45

tat gat gca tcc aga agg gca act ggc atc cca gcc agg ttc agt ggc 192  
 Tyr Asp Ala Ser Arg Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly  
                     50                                    55                                    60

agt ggg tct ggg aca gac ttc act ctc acc atc agc agc cta gag cct 240  
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
 65                                    70                                    75                                    80

gaa gat ttt gca gtt tat tac tgt cag cag cgt aac aac tgg ccg ctc 288  
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Leu  
                     85                                    90                                    95

act ttc ggt gga ggg acc aag gtg gag atc aaa 321  
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                     100                                    105

<210> 80  
 <211> 107  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 80

Glu Thr Thr Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

Gln Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Asn Tyr  
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

Tyr Asp Ala Ser Arg Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Leu  
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105

<210> 81  
<211> 321  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(321)

<400> 81  
gac atc cag ttg acc cag tct cca tcc tcc ctg tct gct tct gtt gga 48  
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
1 5 10 15  
gac agc gtc acc atc tct tgc cgg gca agt cag agt cct ggc atc ttt 96  
Asp Ser Val Thr Ile Ser Cys Arg Ala Ser Gln Ser Pro Gly Ile Phe  
20 25 30  
tta aat tgg tat cag cag ata cca ggg aaa gcc cct aaa ctc ctg atc 144  
Leu Asn Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile  
35 40 45  
tac gct aca tcc act ctg gaa agt ggg gtc ccc ccc agg ttc acc ggc 192  
Tyr Ala Thr Ser Thr Leu Glu Ser Gly Val Pro Pro Arg Phe Thr Gly  
50 55 60  
agt gga tct ggg aca gat ttc act ctc acc atc agc agt ctg caa cct 240  
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80

gag gac ttt gca act tac tac tgt caa cag agt aac agt gtt ccg ctc 288  
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Ser Val Pro Leu  
                   85                                  90                                  95

act ttc ggc ggc ggg acc aag gtg gag atc aaa 321  
 Thr Phe Gly Gly Thr Lys Val Glu Ile Lys  
                   100                                  105

<210> 82  
 <211> 107  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 82

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1                                  5                                  10                                  15

Asp Ser Val Thr Ile Ser Cys Arg Ala Ser Gln Ser Pro Gly Ile Phe  
                   20                                  25                                  30

Leu Asn Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile  
                   35                                  40                                  45

Tyr Ala Thr Ser Thr Leu Glu Ser Gly Val Pro Pro Arg Phe Thr Gly  
                   50                                  55                                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65                                  70                                  75                                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Ser Val Pro Leu  
                   85                                  90                                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                   100                                  105

<210> 83  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 83  
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15  
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30  
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45  
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60  
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca cta aaa atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80  
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
85 90 95  
cta caa act cct cta acc ttc ggc caa ggg aca cga ctg gag att aaa 336  
Leu Gln Thr Pro Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105 110

<210> 84  
<211> 112  
<212> PRT  
<213> Artificial

<220>  
<223> Synthetic Construct

<400> 84  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45  
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala

85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105 110

<210> 85  
<211> 321  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(321)

<400> 85  
gaa att gtg atg acg cag tct cca gcc acc ctg tct gtg tct cca ggg 48  
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly  
1 5 10 15  
gaa aga gcc acc ttc tcc tgt agg gcc agt cag agt gtt ggc agc aac 96  
Glu Arg Ala Thr Phe Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Asn  
20 25 30  
tta gcc tgg tac cag cag aaa cct ggc cag gct ccc agg ctc ctc atc 144  
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45  
tat gat gca tcc aac agg gcc act ggc atc cca gcc agg ttc agt ggc 192  
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly  
50 55 60  
agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag cct 240  
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro  
65 70 75 80  
gaa gat ttt gca gtg tat tac tgt cag cag cgt agc aac tgg ccc ctc 288  
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu  
85 90 95  
act ttc ggc gga ggg acc aag gtg gag atc aaa 321  
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105

<210> 86  
<211> 107  
<212> PRT  
<213> Artificial

<220>  
<223> Synthetic Construct

<400> 86  
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly

1			5			10			15						
Glu	Arg	Ala	Thr 20	Phe	Ser	Cys	Arg	Ala 25	Ser	Gln	Ser	Val	Gly 30	Ser	Asn
Leu	Ala	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Gln	Ala	Pro	Arg 45	Leu	Leu	Ile
Tyr	Asp 50	Ala	Ser	Asn	Arg	Ala 55	Thr	Gly	Ile	Pro	Ala 60	Arg	Phe	Ser	Gly
Ser 65	Gly	Ser	Gly	Thr	Asp 70	Phe	Thr	Leu	Thr	Ile 75	Ser	Arg	Leu	Glu	Pro 80
Glu	Asp	Phe	Ala	Val 85	Tyr	Tyr	Cys	Gln	Gln 90	Arg	Ser	Asn	Trp	Pro 95	Leu
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu 105	Ile	Lys					

<210>	87
<211>	336
<212>	DNA
<213>	Artificial

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<220>
<223> light chain variable region
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<220>
<221> CDS
<222> (1) .. (336)
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<400> 87																
gat	gtt	gtg	atg	act	cag	tct	cca	ctc	tcc	ctg	ccc	gtc	acc	cct	gga	48
Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly	
1				5					10					15		
gag	ccg	gcc	tcc	atc	tcc	tgc	agg	tct	agt	cag	agc	ctc	ctg	cat	agt	96
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser	
			20					25					30			
aat	gga	tac	aac	tat	ttg	gat	tgg	tac	ctg	cag	aag	cca	ggg	cag	tct	144
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	
		35					40					45				
cca	cag	ctc	ctg	atc	tat	ttg	ggt	tct	aat	cgg	gcc	tcc	ggg	gtc	cct	192
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro	
	50					55					60					
gac	agg	ttc	agt	ggc	agt	gga	tca	ggc	aca	gat	ttt	aca	ctg	aaa	atc	240
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	
65				70					75					80		



agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                   85                                  90                                  95

cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                   100                                  105                                  110

<210> 88  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 88

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                  5                                  10                                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
                   20                                  25                                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
                   35                                  40                                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
                   50                                  55                                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65                                  70                                  75                                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                   85                                  90                                  95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                   100                                  105                                  110

<210> 89  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 89

gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly .  
 1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

cca cag ctc ctg atc tac ttg ggt tct act cgg gcc tcc ggc gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro  
 50 55 60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

cta caa act cct tac act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 90  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 90

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Leu Gln Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 91  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 91  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95  
 cta caa act ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 92  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 92

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 93  
<211> 336  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(336)

<400> 93  
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15  
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat act 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr  
20 25 30  
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45  
cca cgg ctc ctg atc tat ttg ggt ttt aat cgg gcc tcc ggg gtc cct 192  
Pro Arg Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro  
50 55 60  
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80  
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgt atg caa ggt 288

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
                     85                    90                    95  
 cta caa act ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa 336  
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                     100                    105                    110

<210> 94  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 94

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                    5                    10                    15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr  
                     20                    25                    30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
                     35                    40                    45

Pro Arg Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro  
                     50                    55                    60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65                    70                    75                    80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
                     85                    90                    95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
                     100                    105                    110

<210> 95  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 95  
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 agc agg gtg gag gct gag gat gtt ggg gtt tat tat tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95  
 aca cac tgg ccg tac act ttt ggc cag ggg acc aag ctg gag atc aaa 336  
 Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 100 105 110

<210> 96  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 96

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 100 105 110

<210> 97  
 <211> 330  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(330)

<400> 97  
 aat ttt atg ctg act cag ccc cac tct gtg tgg gag tct ccg ggg aag 48  
 Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys  
 1 5 10 15  
 acg gta agc atc tcc tgc acc cgc aac agt ggc agc att gcc agc aac 96  
 Thr Val Ser Ile Ser Cys Thr Arg Asn Ser Gly Ser Ile Ala Ser Asn  
 20 25 30  
 ttt gtg cag tgg tac cag cag cgc ccg ggc agt gcc ccc acc att gta 144  
 Phe Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Ile Val  
 35 40 45  
 atc tat gag gat aac caa aga ccc tct gcg gtc cct act cgg ttc tct 192  
 Ile Tyr Glu Asp Asn Gln Arg Pro Ser Ala Val Pro Thr Arg Phe Ser  
 50 55 60  
 ggc tcc atc gac agg tcc tcc aac tct gcc tcc ctc acc atc tct gga 240  
 Gly Ser Ile Asp Arg Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly  
 65 70 75 80  
 ctg acg act gag gac gag gct gac tac tac tgt cag tct tat gat agc 288  
 Leu Thr Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser  
 85 90 95  
 gcc aat gtc att ttc ggc ggg ggg acc aag ctg acc gtc cta 330  
 Ala Asn Val Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105 110

<210> 98  
 <211> 110  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 98

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys  
 1 5 10 15

Thr Val Ser Ile Ser Cys Thr Arg Asn Ser Gly Ser Ile Ala Ser Asn  
20 25 30

Phe Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Ile Val  
35 40 45

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Ala Val Pro Thr Arg Phe Ser  
50 55 60

Gly Ser Ile Asp Arg Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly  
65 70 75 80

Leu Thr Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser  
85 90 95

Ala Asn Val Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105 110

<210> 99  
<211> 324  
<212> DNA  
<213> Artificial

<220>  
<223> light chain variable region

<220>  
<221> CDS  
<222> (1)..(324)

<400> 99  
gaa acg aca ctc acg cag tct cca ggc acc ctg tct ttg tct cca ggg 48  
Glu Thr Thr Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15  
gag aga gcc acc ctc tcc tgc agg gcc agt cag act atc agc agc agc 96  
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Ser Ser Ser  
20 25 30  
cac tta gcc tgg tac cag cag aaa cct ggc cag tct ccc agg ctc ctc 144  
His Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Arg Leu Leu  
35 40 45  
atc tat ggt gcg ggc tac agg gcc acc ggc att cca gac agg ttc agt 192  
Ile Tyr Gly Ala Gly Tyr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser  
50 55 60  
ggc agt ggg tct ggc aca gac ttc act ctc acc atc agc aga ctg gag 240  
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80  
cct gaa gat ttt gca gtg tat tac tgt cag cac tat ggt agt tca ctc 288  
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Ser Leu



85 90 95 324

cgg acg ttc ggc caa ggg acc aag gtg gaa atc aaa  
 Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 100  
 <211> 108  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 100

Glu Thr Thr Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Ser Ser Ser  
 20 25 30

His Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Arg Leu Leu  
 35 40 45

Ile Tyr Gly Ala Gly Tyr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser  
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Ser Leu  
 85 90 95

Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 101  
 <211> 330  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(330)

<400> 101 48

aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag  
 Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys

1	5	10	15	
acg gta acc atc tcc tgc acc ggc agc ggt ggc aac att gcc agc aat				96
Thr Val Thr Ile Ser Cys Thr Gly Ser Gly Gly Asn Ile Ala Ser Asn				
	20	25	30	
tat gtg cag tgg tac cag cag cgc ccg ggc agg gcc ccc acc act gtg				144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Arg Ala Pro Thr Thr Val				
	35	40	45	
atc tat gag gat aat cga aga ccc tct ggc gtc cct gat cgg ttc tct				192
Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser				
	50	55	60	
ggc tcc atc gac agc tcc tcc aac tct gcc tcc ctc acc atc tct gga				240
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly				
	65	70	75	80
ctg aag act gaa gac gag gct gac tac tac tgt cag tct tat gat ccc				288
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro				
	85	90	95	
tac aat cga gtg ttc ggc gga ggg acc aag ctg acc gtc cta				330
Tyr Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu				
	100	105	110	

&lt;210&gt; 102

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 102

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1 5 10 15

Thr Val Thr Ile Ser Cys Thr Gly Ser Gly Gly Asn Ile Ala Ser Asn
20 25 30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Arg Ala Pro Thr Thr Val
35 40 45

Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65 70 75 80

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro
85 90 95

Tyr Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
                   100                                  105                                  110

<210> 103  
 <211> 336  
 <212> DNA  
 <213> Artificial

<220>  
 <223> light chain variable region

<220>  
 <221> CDS  
 <222> (1)..(336)

<400> 103  
 gaa att gtg atg acg cag tct cca ctc tcc ctg ccc gtc acc cct gga 48  
 Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                  5                                  10                                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat act 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr  
                   20                                  25                                  30

aat gga tac gac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144  
 Asn Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
                   35                                  40                                  45

cca cag ctt ctg atc tat ttg ggt tct act cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro  
                   50                                  55                                  60

gac agg ttc agt ggc agt gga tgc ggc aca gat ttt aca ctg aaa atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65                                  70                                  75                                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
                   85                                  90                                  95

ttt caa act ccg ctc act ttc ggc gga ggg acc aag atg gag atc aaa 336  
 Phe Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Met Glu Ile Lys  
                   100                                  105                                  110

<210> 104  
 <211> 112  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 104

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1                  5                                  10                                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr  
 20 25 30

Asn Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala  
 85 90 95

Phe Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Met Glu Ile Lys  
 100 105 110

<210> 105  
 <211> 351  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(351)

<400> 105  
 gag gtg cag ctg gtg gag acc ggc cca gga ctg gtg aag cct tcg ggg 48  
 Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60  
 aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80  
 ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga ttt aat tac tat gat agt agt gtc tgg ggc cag gga acc ctg 336  
 Ala Arg Phe Asn Tyr Tyr Asp Ser Ser Val Trp Gly Gln Gly Thr Leu  
                   100                                  105                                  110

gtc acc gtc tca agc 351  
 Val Thr Val Ser Ser  
                   115

<210> 106  
 <211> 117  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 106

Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1                                  5                                  10                                  15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
                   20                                  25                                  30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
                   35                                  40                                  45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
                   50                                  55                                  60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65                                  70                                  75                                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                   85                                  90                                  95

Ala Arg Phe Asn Tyr Tyr Asp Ser Ser Val Trp Gly Gln Gly Thr Leu  
                   100                                  105                                  110

Val Thr Val Ser Ser  
                   115

<210> 107  
 <211> 348  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(348)

&lt;400&gt; 107

gag	gtg	cag	ctg	gtg	gag	acc	ggc	cca	gga	ctg	gtg	aag	cct	tcg	ggg	48
Glu	Val	Gln	Leu	Val	Glu	Thr	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gly	
1				5					10					15		

acc	ctg	tcc	ctc	acc	tgc	gct	gtc	tct	ggg	ggc	tcc	atc	agc	agt	agt	96
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser	
			20					25					30			

aac	tgg	tgg	agt	tgg	gtc	cgc	cag	ccc	cca	ggg	aag	ggg	ctg	gag	tgg	144
Asn	Trp	Trp	Ser	Trp	Val	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	
		35					40					45				

att	ggg	gaa	atc	tat	cat	agt	ggg	agc	acc	aac	tac	aac	ccg	tcc	ctc	192
Ile	Gly	Glu	Ile	Tyr	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	
	50					55					60					

aag	agt	cga	gtc	acc	ata	tca	gta	gac	aag	tcc	aag	aac	cag	ttc	tcc	240
Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Lys	Ser	Lys	Asn	Gln	Phe	Ser	
65					70				75					80		

ctg	aag	ctg	agc	tct	gtg	acc	gcc	gcg	gac	acg	gcc	gtg	tat	tac	tgt	288
Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		

gcg	aga	ggg	gtt	gag	cag	att	gac	tac	tgg	ggc	cag	gga	acc	ctg	gtc	336
Ala	Arg	Gly	Val	Glu	Gln	Ile	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	
			100				105						110			

acc	gtc	tca	agc													348
Thr	Val	Ser	Ser													
			115													

&lt;210&gt; 108

&lt;211&gt; 116

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 108

Glu	Val	Gln	Leu	Val	Glu	Thr	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gly
1				5					10					15	

Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser
			20					25					30		

Asn	Trp	Trp	Ser	Trp	Val	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
		35					40					45			

Ile	Gly	Glu	Ile	Tyr	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

50                                      55                                      60  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65                                      70                                      75                                      80  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                                     85                                      90                                      95  
 Ala Arg Gly Val Glu Gln Ile Asp Tyr Trp Gly Gln Gly Thr Leu Val  
                                     100                                      105                                      110  
 Thr Val Ser Ser  
                                     115  
 .  
 <210> 109  
 <211> 354  
 <212> DNA  
 <213> Artificial  
 <220>  
 <223> heavy chain variable region  
 <220>  
 <221> CDS  
 <222> (1)..(354)  
 <400> 109  
 cag gtg cag ctg cag gag tgc ggc cca gga ctg gtg aag cct tgc ggg 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1                                      5                                      10                                      15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
                                     20                                      25                                      30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
                                     35                                      40                                      45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
                                     50                                      55                                      60  
 aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65                                      70                                      75                                      80  
 ctg aag ctg agc tct gtg act gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                                     85                                      90                                      95  
 gcg aaa aat tta gca gca ggg gcg gtt gcc tac tgg ggc cag ggc acc 336  
 Ala Lys Asn Leu Ala Ala Gly Ala Val Ala Tyr Trp Gly Gln Gly Thr  
                                     100                                      105                                      110

ctg gtc acc gtc tca agc  
 Leu Val Thr Val Ser Ser  
 115

354

<210> 110  
 <211> 118  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 110

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Asn Leu Ala Ala Gly Ala Val Ala Tyr Trp Gly Gln Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser  
 115

<210> 111  
 <211> 351  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(351)  
 <400> 111



cag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag 48  
 Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
 1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggg tcc ttc agt ggt tac 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Phe Ser Gly Tyr  
 20 25 30

tac tgg agc tgg atc cgt cag ccc cca ggg aag ggg ctg gag tgg att 144  
 Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
 35 40 45

ggg gaa atc aat cat agt gga agt acc aac tac aac cgg tcc ctc aag 192  
 Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Arg Ser Leu Lys  
 50 55 60

agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc ctg 240  
 Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65 70 75 80

aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg 288  
 Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
 85 90 95

aga ctt tca tat ggt tcg ggc gtt gac tac tgg ggc cag ggc acc ctg 336  
 Arg Leu Ser Tyr Gly Ser Gly Val Asp Tyr Trp Gly Gln Gly Thr Leu  
 100 105 110

gtc acc gtc tca agc 351  
 Val Thr Val Ser Ser  
 115

<210> 112  
 <211> 117  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 112

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Phe Ser Gly Tyr  
 20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
 35 40 45

Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Arg Ser Leu Lys  
 50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Arg Leu Ser Tyr Gly Ser Gly Val Asp Tyr Trp Gly Gln Gly Thr Leu  
100 105 110

Val Thr Val Ser Ser  
115

<210> 113  
<211> 360  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(360)

<400> 113  
cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tca cag 48  
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln  
1 5 10 15  
acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80  
ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg agg tat agc agc agc cgc aat gat gct ttt gat atc tgg ggc caa 336  
Ala Arg Tyr Ser Ser Ser Arg Asn Asp Ala Phe Asp Ile Trp Gly Gln  
100 105 110  
ggg aca atg gtc acc gtc tca agc 360  
Gly Thr Met Val Thr Val Ser Ser  
115 120

<210> 114  
 <211> 120  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 114

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Tyr Ser Ser Ser Arg Asn Asp Ala Phe Asp Ile Trp Gly Gln  
 100 105 110

Gly Thr Met Val Thr Val Ser Ser  
 115 120

<210> 115  
 <211> 354  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(354)

<400> 115  
 cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga gat ggg cag ctg gat gct ttt gat atc tgg ggc caa ggg aca 336  
 Ala Arg Asp Gly Gln Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
 100 105 110

atg gtc acc gtc tca agc 354  
 Met Val Thr Val Ser Ser  
 115

<210> 116  
 <211> 118  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 116

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Gly Gln Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
 100 105 110

Met Val Thr Val Ser Ser  
 115

<210> 117  
 <211> 354  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(354)

<400> 117  
 cag gtg cag ctg cag gag tgc ggc cca gga ctg gtg aag cct tgc ggg 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60  
 aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80  
 ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga ttt tgg gac tac tac ggt atg gac gtc tgg ggc caa ggg acc 336  
 Ala Arg Phe Trp Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr  
 100 105 110  
 acg gtc acc gtc tca agc 354  
 Thr Val Thr Val Ser Ser  
 115

<210> 118  
 <211> 118  
 <212> PRT  
 <213> Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 118

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Phe Trp Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr  
100 105 110

Thr Val Thr Val Ser Ser  
115

&lt;210&gt; 119

&lt;211&gt; 351

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(351)

&lt;400&gt; 119

cag gtg cag cta cag cag tgg ggc cca gga ctg gtg aag cct tcc ggg 48  
Gln Val Gln Leu Gln Gln Trp Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp

[illegible]

Val Thr Val Ser Ser  
115

<210> 121  
<211> 354  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(354)

<400> 121  
gag gtg cag ctg gtc gag tct ggc cca gga ctg gtg aag cct tcg ggg 48  
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg tac atc tat tat agt ggg agc acc tac tac aac ccg tcc ctc 192  
Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc atg tca gta gac acg tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser  
65 70 75 80  
ctg aag ctg agc tct gtg acc gcc gca gac acg gcc gtg tat tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg aga tgg agc tac ttg gat gct ttt gat atc tgg ggc caa ggg aca 336  
Ala Arg Trp Ser Tyr Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
100 105 110  
atg gtc acc gtc tca agc 354  
Met Val Thr Val Ser Ser  
115

<210> 122  
<211> 118  
<212> PRT  
<213> Artificial  
  
<220>  
<223> Synthetic Construct  
  
<400> 122



Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45

Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu  
50 55 60

Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser  
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Trp Ser Tyr Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
100 105 110

Met Val Thr Val Ser Ser  
115

<210> 123  
<211> 354  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(354)

<400> 123  
gag gtg cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg 48  
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga gat tac gat att ttc ggt atg gac gtc tgg ggc caa ggg acc 336  
 Ala Arg Asp Tyr Asp Ile Phe Gly Met Asp Val Trp Gly Gln Gly Thr  
 100 105 110

acg gtc acc gtc tca agc 354  
 Thr Val Thr Val Ser Ser  
 115

<210> 124  
 <211> 118  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 124

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Tyr Asp Ile Phe Gly Met Asp Val Trp Gly Gln Gly Thr  
 100 105 110

Thr Val Thr Val Ser Ser  
 115

<210> 125

<211> 354  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1) .. (354)

<400> 125  
 cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg 48  
 Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60  
 aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag tcc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Ser Ser  
 65 70 75 80  
 ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga gcc aac aga gat gat gct ttt gat atc tgg ggc caa ggg aca 336  
 Ala Arg Ala Asn Arg Asp Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
 100 105 110  
 atg gtc acc gtc tca agc 354  
 Met Val Thr Val Ser Ser  
 115

<210> 126  
 <211> 118  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 126

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser

20 25 30  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Ser Ser  
 65 70 75 80  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Ala Asn Arg Asp Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
 100 105 110  
 Met Val Thr Val Ser Ser  
 115

<210> 127  
 <211> 357  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(357)

<400> 127  
 gag gtg cag ctg gtg gag tct ggg gga ggc ttg gta cag ccg ggg ggg 48  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agc agc tat 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 tca gct att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg 192  
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

ctg caa atg aac agt ctg agc gcc gac gac acg gcc gta tat ttc tgt 288  
 Leu Gln Met Asn Ser Leu Ser Ala Asp Asp Thr Ala Val Tyr Phe Cys  
                   85                                  90                                  95

gcg tcg ggt ggc tgg tac ggg gac tac ttt gac tac tgg ggc cag gga 336  
 Ala Ser Gly Gly Trp Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly  
                   100                                  105                                  110

acc ctg gtc acc gtc tca agc 357  
 Thr Leu Val Thr Val Ser Ser  
                   115

<210> 128  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 128

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1                  5                                  10                                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
                   20                                  25                                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                   35                                  40                                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
                   50                                  55                                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65                                  70                                  75                                  80

Leu Gln Met Asn Ser Leu Ser Ala Asp Asp Thr Ala Val Tyr Phe Cys  
                   85                                  90                                  95

Ala Ser Gly Gly Trp Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly  
                   100                                  105                                  110

Thr Leu Val Thr Val Ser Ser  
                   115

<210> 129  
 <211> 363  
 <212> DNA  
 <213> Artificial

<220>

<223> heavy chain variable region

<220>

<221> CDS

<222> (1)..(363)

<400> 129

cag	gtg	cag	ctg	cag	gag	tcc	ggc	cca	gga	ctg	gtg	aag	cct	tcg	gag	48
Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu	
1				5				10						15		

acc	ctg	tcc	ctc	acc	tgc	act	gtc	tct	ggg	ggc	tcc	atc	agc	agt	agt	96
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser	
			20					25					30			

aac	tgg	tgg	agt	tgg	gtc	cgc	cag	ccc	cca	ggg	aag	ggg	ctg	gag	tgg	144
Asn	Trp	Trp	Ser	Trp	Val	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	
			35				40					45				

att	ggg	gaa	atc	tat	cat	agt	ggg	agc	acc	aac	tac	aac	ccg	tcc	ctc	192
Ile	Gly	Glu	Ile	Tyr	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	
	50					55					60					

aag	agt	cga	gtc	acc	ata	tca	gta	gac	aag	tcc	aag	aac	cag	ttc	tcc	240
Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Lys	Ser	Lys	Asn	Gln	Phe	Ser	
65					70				75					80		

ctg	aag	ctg	agc	tct	gtg	acc	gcc	gcg	gac	acg	gcc	gtg	tat	tac	tgt	288
Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		

gcg	aga	gaa	ggg	aac	cga	acg	gtg	act	agt	gct	ttt	gat	atc	tgg	ggc	336
Ala	Arg	Glu	Gly	Asn	Arg	Thr	Val	Thr	Ser	Ala	Phe	Asp	Ile	Trp	Gly	
			100					105					110			

caa	ggg	aca	atg	gtc	acc	gtc	tca	agc								363
Gln	Gly	Thr	Met	Val	Thr	Val	Ser	Ser								
			115				120									

<210> 130

<211> 121

<212> PRT

<213> Artificial

<220>

<223> Synthetic Construct

<400> 130

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5				10						15	

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser
			20					25					30		

Asn	Trp	Trp	Ser	Trp	Val	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
			35				40					45			

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Glu Gly Asn Arg Thr Val Thr Ser Ala Phe Asp Ile Trp Gly  
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser  
115 120

<210> 131  
<211> 357  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(357)

<400> 131  
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80  
ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tac tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg aga ggg ctg ggg gat agt agt ggt tat atc ctt tgg ggc caa ggg 336

Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly  
 100 105 110

aca atg gtc acc gtc tca agc  
 Thr Met Val Thr Val Ser Ser  
 115

357

<210> 132  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 132

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly  
 100 105 110

Thr Met Val Thr Val Ser Ser  
 115

<210> 133  
 <211> 357  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS



&lt;222&gt; (1)..(357)

&lt;400&gt; 133

cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tac tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga ggg ctg ggg gat agt agt ggt tat atc ctt tgg ggc caa ggg 336  
 Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly  
 100 105 110

aca atg gtc acc gtc tca agc 357  
 Thr Met Val Thr Val Ser Ser  
 115

&lt;210&gt; 134

&lt;211&gt; 119

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 134

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly  
100 105 110

Thr Met Val Thr Val Ser Ser  
115

<210> 135

<211> 357

<212> DNA

<213> Artificial

<220>

<223> heavy chain variable region

<220>

<221> CDS

<222> (1)..(357)

<400> 135

cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

gcg aga tgg acc ggg cgt act gat gct ttt gat atc tgg ggc caa ggg 336  
Ala Arg Trp Thr Gly Arg Thr Asp Ala Phe Asp Ile Trp Gly Gln Gly  
100 105 110

aca atg gtc acc gtc tca agc 357  
Thr Met Val Thr Val Ser Ser

115

<210> 136  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 136

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Trp Thr Gly Arg Thr Asp Ala Phe Asp Ile Trp Gly Gln Gly  
 100 105 110

Thr Met Val Thr Val Ser Ser  
 115

<210> 137  
 <211> 354  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(354)

<400> 137  
 cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly

48

1	5	10	15	
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt				96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser	20	25	30	
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg				144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp	35	40	45	
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc				192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu	50	55	60	
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc				240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser	65	70	75	80
ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt				288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys	85	90	95	
gcg aga caa ggg gcg tta gat gct ttt gat atc tgg ggc caa ggg acc				336
Ala Arg Gln Gly Ala Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr	100	105	110	
acg gtc acc gtc tca agc				354
Thr Val Thr Val Ser Ser	115			

&lt;210&gt; 138

&lt;211&gt; 118

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 138

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly			
1	5	10	15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser			
20	25	30	

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp			
35	40	45	

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu			
50	55	60	

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser			
65	70	75	80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                     85                    90                    95

Ala Arg Gln Gly Ala Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
                     100                    105                    110

Thr Val Thr Val Ser Ser  
                     115

<210> 139  
 <211> 366  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(366)

<400> 139  
 cag gtg cag ctg gtg gag tcc ggg gga ggc gtg gtc cga cct ggg ggg 48  
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly  
 1                    5                    10                    15  
 tcc ctg aga ctc tcc tgt gca gcg tct gga ttc acc ttt agc agc tat 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
                     20                    25                    30  
 gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                     35                    40                    45  
 tca act att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg 192  
 Ser Thr Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
                     50                    55                    60  
 aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65                    70                    75                    80  
 ctg cag atg aac agc ctg aga gcc gag gac acg gcc gta tat tac tgt 288  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
                     85                    90                    95  
 gcg aaa gag cgt ggc agt ggc tgg tcc tta gac aat atg gac gtc tgg 336  
 Ala Lys Glu Arg Gly Ser Gly Trp Ser Leu Asp Asn Met Asp Val Trp  
                     100                    105                    110  
 ggc caa ggg acc acg gtc acc gtc tca agc 366  
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
                     115                    120

<210> 140  
 <211> 122

<212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 140

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ser Thr Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Glu Arg Gly Ser Gly Trp Ser Leu Asp Asn Met Asp Val Trp  
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> 141  
 <211> 357  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(357)

<400> 141

cag gtg cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg 48  
 Gln Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
           35                          40                          45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
           50                          55                          60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
           65                          70                          75                          80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                           85                          90                          95

gcg aga gat agc agt ggg ttc tac ggt atg gac gtc tgg ggc caa ggg 336  
 Ala Arg Asp Ser Ser Gly Phe Tyr Gly Met Asp Val Trp Gly Gln Gly  
                           100                          105                          110

acc acg gtc acc gtc tca agc 357  
 Thr Thr Val Thr Val Ser Ser  
           115

<210> 142  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 142

Gln Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1                          5                          10                          15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
           20                          25                          30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
           35                          40                          45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
           50                          55                          60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65                          70                          75                          80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
           85                          90                          95

Ala Arg Asp Ser Ser Gly Phe Tyr Gly Met Asp Val Trp Gly Gln Gly

100 105 110

Thr Thr Val Thr Val Ser Ser  
115

<210> 143  
<211> 360  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(360)

<400> 143  
cag gtg cag ctg cag gag tgc ggc cca gga ctg gtg aag cct tcg ggg 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80  
ctg aag ctg agc tct gtg act gcc gcg gac acg gcc gtg tat tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg aga agc agc agc tgg tac tgg aat gct ttt gat atc tgg ggc caa 336  
Ala Arg Ser Ser Ser Trp Tyr Trp Asn Ala Phe Asp Ile Trp Gly Gln  
100 105 110  
ggg aca atg gtc acc gtc tca agc 360  
Gly Thr Met Val Thr Val Ser Ser  
115 120

<210> 144  
<211> 120  
<212> PRT  
<213> Artificial

<220>  
<223> Synthetic Construct



&lt;400&gt; 144

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Ser Ser Ser Trp Tyr Trp Asn Ala Phe Asp Ile Trp Gly Gln  
 100 105 110

Gly Thr Met Val Thr Val Ser Ser  
 115 120

&lt;210&gt; 145

&lt;211&gt; 351

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(351)

&lt;400&gt; 145

cag gtg cag cta cag cag tgg ggc cca gca ctg gtg aag cct tcg ggg 48  
 Gln Val Gln Leu Gln Gln Trp Gly Pro Ala Leu Val Lys Pro Ser Gly  
 1 5 10 15

acc ctg tcc ctc acc tgc tct gtc tct ggt gtc tcc atc acc agt aat 96  
 Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Val Ser Ile Thr Ser Asn  
 20 25 30

atc tgg tgg agt tgg gtc cgc cag tcc cca ggg aag ggg ctg gag tgg 144  
 Ile Trp Trp Ser Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

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att ggg gaa gtc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
Ile Gly Glu Val Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
   50                      55                      60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
   65                      70                      75                      80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
   85                      90                      95

gcg ggg tac cgt agc ttc ggg gag tcc tac tgg ggc cag gga acc ctg      336
Ala Gly Tyr Arg Ser Phe Gly Glu Ser Tyr Trp Gly Gln Gly Thr Leu
   100                      105                      110

gtc acc gtc tca agc
Val Thr Val Ser Ser
   115

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<210> 146
<211> 117
<212> PRT
<213> Artificial

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<220>
<223> Synthetic Construct

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<400> 146

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Gln Val Gln Leu Gln Gln Trp Gly Pro Ala Leu Val Lys Pro Ser Gly
1                      5                      10                      15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Val Ser Ile Thr Ser Asn
20                      25                      30

Ile Trp Trp Ser Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
35                      40                      45

Ile Gly Glu Val Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
50                      55                      60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                      75                      80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85                      90                      95

Ala Gly Tyr Arg Ser Phe Gly Glu Ser Tyr Trp Gly Gln Gly Thr Leu
100                      105                      110

Val Thr Val Ser Ser
115

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<210> 147  
 <211> 366  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1) .. (366)

<400> 147  
 cag gtg cag cta cag cag tgg ggc gca ggg ctg ttg aag cct tcg gag 48  
 Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
 1 5 10 15  
 acc ctg tct ctc acc tgc gtt gtc tat ggt ggg tcc ttc agc gat ttc 96  
 Thr Leu Ser Leu Thr Cys Val Val Tyr Gly Gly Ser Phe Ser Asp Phe  
 20 25 30  
 tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg cca gag tgg att 144  
 Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Pro Glu Trp Ile  
 35 40 45  
 ggg gaa gtc aat cct aga gga agc acc aac tac aac ccg tcc ctc aag 192  
 Gly Glu Val Asn Pro Arg Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
 50 55 60  
 agt cga gcc acc ata tca cta gac acg tcc aag aac cag ttc tcc ctg 240  
 Ser Arg Ala Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65 70 75 80  
 aag ctg agt tct gtg acc gcc gcg gac acg gct gtg tat ttc tgt gcg 288  
 Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala  
 85 90 95  
 aga ggt cct cgg ccc ggg aga gat ggc tac aat tac ttt gac aac tgg 336  
 Arg Gly Pro Arg Pro Gly Arg Asp Gly Tyr Asn Tyr Phe Asp Asn Trp  
 100 105 110  
 ggc cag ggc acc ctg gtc acc gtc tca agc 366  
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> 148  
 <211> 122  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 148

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Val Val Tyr Gly Gly Ser Phe Ser Asp Phe  
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Pro Glu Trp Ile  
35 40 45

Gly Glu Val Asn Pro Arg Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
50 55 60

Ser Arg Ala Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu  
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala  
85 90 95

Arg Gly Pro Arg Pro Gly Arg Asp Gly Tyr Asn Tyr Phe Asp Asn Trp  
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 149  
<211> 357  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(357)

<400> 149  
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
1 5 10 15  
acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80  
 ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga ggt ata gca gca gct ggt caa ggt gac tac tgg ggc cag gga 336  
 Ala Arg Gly Ile Ala Ala Ala Gly Gln Gly Asp Tyr Trp Gly Gln Gly  
 100 105 110  
 acc ctg gtc acc gtc tca agc 357  
 Thr Leu Val Thr Val Ser Ser  
 115

<210> 150  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 150

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Gly Ile Ala Ala Ala Gly Gln Gly Asp Tyr Trp Gly Gln Gly  
 100 105 110  
 Thr Leu Val Thr Val Ser Ser  
 115

<210> 151  
 <211> 363  
 <212> DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(363)

&lt;400&gt; 151

cag	gtg	cag	ctg	cag	gag	tcg	ggc	cca	gga	ctg	gtg	aag	cct	tcg	gag	48
Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu	
1				5					10					15		

acc	ctg	tcc	ctc	acc	tgc	act	gtc	tct	ggg	ggc	tcc	atc	agc	agt	agt	96
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser	
			20					25					30			

agt	tac	tac	tgg	ggc	tgg	atc	cgc	cag	ccc	cca	ggg	aag	ggg	ctg	gag	144
Ser	Tyr	Tyr	Trp	Gly	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	
		35					40					45				

tgg	att	ggg	agt	atc	tat	tat	agt	ggg	agc	acc	tac	tac	aac	ccg	tcc	192
Trp	Ile	Gly	Ser	Ile	Tyr	Tyr	Ser	Gly	Ser	Thr	Tyr	Tyr	Asn	Pro	Ser	
	50					55						60				

ctc	aag	agt	cga	gtc	acc	ata	tcc	gta	gac	acg	tcc	aag	aac	cag	ttc	240
Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	
65					70					75					80	

tcc	ctg	aag	ctg	agc	tct	gtg	acc	gcc	gcg	gac	acg	gcc	gtg	tat	tac	288
Ser	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	
				85					90					95		

tgt	gcg	aga	gat	ggg	gga	tac	tac	tac	tac	ggg	atg	gac	gtc	tgg	ggc	336
Cys	Ala	Arg	Asp	Gly	Gly	Tyr	Tyr	Tyr	Tyr	Gly	Met	Asp	Val	Trp	Gly	
			100					105					110			

caa	ggg	acc	acg	gtc	acc	gtc	tca	agc								363
Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser								
			115				120									

&lt;210&gt; 152

&lt;211&gt; 121

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 152

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5					10					15	

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser
			20					25					30		

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu  
 35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser  
 50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe  
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Gly Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> 153  
 <211> 351  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(351)

<400> 153  
 cag gtg cag ctg cag gag tgc ggc cca gga ctg gtg aag cct tgc ggg 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60  
 aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80  
 ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys

	85	90	95	
gcg agt agt ggt tat gat gct ttt gat atc tgg ggc caa ggg acc acg				336
Ala Ser Ser Gly Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr				
	100	105	110	
gtc acc gtc tca agc				351
Val Thr Val Ser Ser				
	115			

<210> 154  
 <211> 117  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 154

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly				
1	5	10	15	
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser				
	20	25	30	
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp				
	35	40	45	
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu				
	50	55	60	
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser				
	65	70	75	80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys				
	85	90	95	
Ala Ser Ser Gly Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr				
	100	105	110	
Val Thr Val Ser Ser				
	115			

<210> 155  
 <211> 357  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region



&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(357)

&lt;400&gt; 155

cag	gtg	cag	ctg	cag	gag	tcg	ggc	cca	gga	ctg	gtg	aag	cct	tcg	ggg	48
Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gly	
1				5					10					15		

acc	ctg	tcc	ctc	acc	tgc	gct	gtc	tct	ggt	ggc	tcc	atc	agc	agt	agt	96
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser	
			20					25					30			

aat	tgg	tgg	agt	tgg	gtc	cgc	cag	ccc	cca	ggg	aag	ggg	ctg	gag	tgg	144
Asn	Trp	Trp	Ser	Trp	Val	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	
		35					40					45				

att	ggg	gaa	atc	tat	cat	agt	ggg	agc	acc	aac	tac	aac	ccg	tcc	ctc	192
Ile	Gly	Glu	Ile	Tyr	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	
	50					55					60					

aag	agt	cga	gtc	acc	ata	tca	gta	gac	aag	tcc	aag	aac	cag	ttc	tcc	240
Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Lys	Ser	Lys	Asn	Gln	Phe	Ser	
65					70				75					80		

ctg	aag	ctg	agc	tct	gtg	acc	gcc	gcg	gac	acg	gcc	gtg	tat	tac	tgt	288
Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
			85						90					95		

gca	cga	tac	agc	tat	gga	acg	gta	gga	att	gac	tac	tgg	ggc	cag	gga	336
Ala	Arg	Tyr	Ser	Tyr	Gly	Thr	Val	Gly	Ile	Asp	Tyr	Trp	Gly	Gln	Gly	
			100					105					110			

acc	ctg	gtc	acc	gtc	tca	agc										357
Thr	Leu	Val	Thr	Val	Ser	Ser										
			115													

&lt;210&gt; 156

&lt;211&gt; 119

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 156

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gly
1				5					10					15	

Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Ser
			20					25					30		

Asn	Trp	Trp	Ser	Trp	Val	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
		35					40					45			

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Tyr Ser Tyr Gly Thr Val Gly Ile Asp Tyr Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

<210> 157  
<211> 351  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(351)  
<223> heavy chain variable region

<400> 157  
gag gtg cag ctg gtg cag tct ggg gga ggc gtg gtc cag cct ggg acg 48  
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Thr  
1 5 10 15  
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc agc ttc aga agt cat 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Arg Ser His  
20 25 30  
ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg 144  
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45  
gca gtt ata tca tat gat gga agt aat aaa tac tat gca gac tcc gtg 192  
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
50 55 60  
aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80  
ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt 288  
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg act ata ggg ccg ggg gga ttt gac tac tgg ggc cag ggc acc ctg 336  
Ala Thr Ile Gly Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu

100 105 110 351  
 gtc acc gtc tca agc  
 Val Thr Val Ser Ser  
 115  
  
 <210> 158  
 <211> 117  
 <212> PRT  
 <213> Artificial  
  
 <220>  
 <223> Synthetic Construct  
  
 <400> 158  
  
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Thr  
 1 5 10 15  
  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Arg Ser His  
 20 25 30  
  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
  
 Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60  
  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
  
 Ala Thr Ile Gly Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu  
 100 105 110  
  
 Val Thr Val Ser Ser  
 115  
  
 <210> 159  
 <211> 357  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> heavy chain variable region  
  
 <220>  
 <221> CDS  
 <222> (1)..(357)

<400> 159  
 cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg gag 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15  
 acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc att aga aat tac 96  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Asn Tyr  
 20 25 30  
 tac tgg agt tgg atc cgg cag ccc cca ggg aag gga ctg gag tgg att 144  
 Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
 35 40 45  
 ggg tat att tct gac agt ggg aat acc aac tac aat ccc tcc ctc aag 192  
 Gly Tyr Ile Ser Asp Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys  
 50 55 60  
 agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc cta 240  
 Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65 70 75 80  
 aag ctg acc tct gtg acc gcc aca gac acg gct gcg tat ttc tgt gcg 288  
 Lys Leu Thr Ser Val Thr Ala Thr Asp Thr Ala Ala Tyr Phe Cys Ala  
 85 90 95  
 aga cat cga agc agc tgg gca tgg tac ttc gat ctc tgg ggc cgt ggc 336  
 Arg His Arg Ser Ser Trp Ala Trp Tyr Phe Asp Leu Trp Gly Arg Gly  
 100 105 110  
 acc ctg gtc acc gtc tca agc 357  
 Thr Leu Val Thr Val Ser Ser  
 115

<210> 160  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 160  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Asn Tyr  
 20 25 30  
 Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
 35 40 45  
 Gly Tyr Ile Ser Asp Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys  
 50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
65 70 75 80

Lys Leu Thr Ser Val Thr Ala Thr Asp Thr Ala Ala Tyr Phe Cys Ala  
85 90 95

Arg His Arg Ser Ser Trp Ala Trp Tyr Phe Asp Leu Trp Gly Arg Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

<210> 161  
<211> 354  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(354)

<400> 161  
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80  
ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg aga gtg ggc agt ggc tgg tac gtt gac tac tgg ggc cag gga acc 336  
Ala Arg Val Gly Ser Gly Trp Tyr Val Asp Tyr Trp Gly Gln Gly Thr  
100 105 110  
ctg gtc acc gtc tca agc 354  
Leu Val Thr Val Ser Ser  
115

<210> 162  
 <211> 118  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 162

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Val Gly Ser Gly Trp Tyr Val Asp Tyr Trp Gly Gln Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser  
 115

<210> 163  
 <211> 360  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(360)

<400> 163  
 cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

48

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
                   20                                  25                                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
                   35                                  40                                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
                   50                                  55                                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
                   65                                  70                                  75                                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                                   85                                  90                                  95

gcg aga gtt tct ggc tac tac tac tac ggt atg gac gtc tgg ggc caa 336  
 Ala Arg Val Ser Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln  
                                   100                                  105                                  110

ggg acc acg gtc acc gtc tca agc 360  
 Gly Thr Thr Val Thr Val Ser Ser  
                   115                                  120

<210> 164  
 <211> 120  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 164

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1                  5                                  10                                  15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
                   20                                  25                                  30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
                   35                                  40                                  45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
                   50                                  55                                  60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
                   65                                  70                                  75                                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys

	85	90	95	
Ala Arg Val Ser Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln				
	100	105	110	
Gly Thr Thr Val Thr Val Ser Ser				
	115	120		
<210> 165				
<211> 369				
<212> DNA				
<213> Artificial				
<220>				
<223> heavy chain variable region				
<220>				
<221> CDS				
<222> (1)..(369)				
<400> 165				
gag gtc cag ctg gta cag tct ggg gga ggc gtg gtc cag cct ggg agg				48
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg				
1 5 10 15				
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc agt agc tat				96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr				
20 25 30				
ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg				144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val				
35 40 45				
gca gtt ata tca tat gat gga agt aat aaa tac tat gca gac tcc gtg				192
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val				
50 55 60				
aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat				240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr				
65 70 75 80				
ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt				288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys				
85 90 95				
gcg aaa gcg tat agc agt ggc tgg tac gac tac tac ggt atg gac gtc				336
Ala Lys Ala Tyr Ser Ser Gly Trp Tyr Asp Tyr Tyr Gly Met Asp Val				
100 105 110				
tgg ggc caa ggg acc acg gtc acc gtc tca agc				369
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser				
115 120				
<210> 166				
<211> 123				
<212> PRT				



&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 166

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Lys Ala Tyr Ser Ser Gly Trp Tyr Asp Tyr Tyr Gly Met Asp Val  
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
115 120

&lt;210&gt; 167

&lt;211&gt; 351

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(351)

&lt;400&gt; 167

cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30

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aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg      144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
      35                      40                      45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
      50                      55                      60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
      65                      70                      75

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
      85                      90                      95

gcg aga gcc agc gtt gat gct ttt gat atc tgg ggc caa ggg aca atg      336
Ala Arg Ala Ser Val Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
      100                      105                      110

gtc acc gtc tca agc
Val Thr Val Ser Ser
      115

<210> 168
<211> 117
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 168

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1                      5                      10                      15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
      20                      25                      30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
      35                      40                      45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
      50                      55                      60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
      65                      70                      75                      80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
      85                      90                      95

Ala Arg Ala Ser Val Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
      100                      105                      110

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Val Thr Val Ser Ser  
115

<210> 169  
<211> 357  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(357)

<400> 169  
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80  
ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tac tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg aga ggg ctg ggg gat agt agt ggt tat atc ctt tgg ggc caa ggg 336  
Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly  
100 105 110  
aca atg gtc acc gtc tca agc 357  
Thr Met Val Thr Val Ser Ser  
115

<210> 170  
<211> 119  
<212> PRT  
<213> Artificial

<220>  
<223> Synthetic Construct

&lt;400&gt; 170

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly  
 100 105 110

Thr Met Val Thr Val Ser Ser  
 115

<210> 171  
 <211> 348  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(348)

<400> 171  
 cag gta cag ctg cag cag tca ggc cca gga ctg gtg aag cct tcg ggg 48  
 Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192

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Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
 50                      55                      60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                      75                      80

ctg aag ctg agc tct gtg act ccc gag gac acg gct gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                        85                      90                      95

gca aga gat cac ggc ccc ttt gac tac tgg ggc cgg gga acc ctg gtc      336
Ala Arg Asp His Gly Pro Phe Asp Tyr Trp Gly Arg Gly Thr Leu Val
                        100                      105                      110

acc gtc tca agc
Thr Val Ser Ser
                        115

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<210> 172
<211> 116
<212> PRT
<213> Artificial

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<220>
<223> Synthetic Construct

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<400> 172

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Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1                      5                      10                      15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                      25                      30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35                      40                      45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
50                      55                      60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                      75                      80

Leu Lys Leu Ser Ser Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                        85                      90                      95

Ala Arg Asp His Gly Pro Phe Asp Tyr Trp Gly Arg Gly Thr Leu Val
100                      105                      110

Thr Val Ser Ser
115

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<210> 173  
 <211> 360  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(360)

<400> 173  
 cag gtg cag ctg gtg caa tct ggg gga ggc gtg gtc cag cct ggg agg 48  
 Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 tcc ctg aga ctc tcc tgt gca gcc tct gga ttc gcc ttc agt agc tat 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr  
 20 25 30  
 ggc atg cac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtt 144  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 tca tac att agt agt agt agt agt acc ata tac tac gca gac tct gtg 192  
 Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 ctg caa atg aac agc ctg aga gcc gag gac acg gct gtg tat tac tgt 288  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga gat cga ttt ggg tcg ggg cac ttg ccc gac tac tgg ggc cag 336  
 Ala Arg Asp Arg Phe Gly Ser Gly His Leu Pro Asp Tyr Trp Gly Gln  
 100 105 110  
 gga acc ctg gtc acc gtc tca agc 360  
 Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> 174  
 <211> 120  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 174

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr  
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Asp Arg Phe Gly Ser Gly His Leu Pro Asp Tyr Trp Gly Gln  
100 105 110

Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 175  
<211> 357  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(357)

<400> 175  
cag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag 48  
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tat ggt ggg tcc ttc agt ggt tac 96  
Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr  
20 25 30  
tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg ctg gag tgg att 144  
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
35 40 45  
ggg gaa atc aat cat agt gga agc acc aac tac aac ccg tcc ctc aag 192  
Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
50 55 60  
agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc ctg 240  
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu

65	70	75	80	
aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg				288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala	85	90	95	
aga gtt ggg tat agc agt ggc cgt gac gtt gac tac tgg ggc cag ggc				336
Arg Val Gly Tyr Ser Ser Gly Arg Asp Val Asp Tyr Trp Gly Gln Gly	100	105	110	
acc ctg gtc acc gtc tca agc				357
Thr Leu Val Thr Val Ser Ser	115			

<210> 176  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 176

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu			
1	5	10	15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr			
20	25	30	

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile			
35	40	45	

Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys			
50	55	60	

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu			
65	70	75	80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala			
85	90	95	

Arg Val Gly Tyr Ser Ser Gly Arg Asp Val Asp Tyr Trp Gly Gln Gly			
100	105	110	

Thr Leu Val Thr Val Ser Ser	
115	

<210> 177  
 <211> 360  
 <212> DNA  
 <213> Artificial



&lt;220&gt;

&lt;223&gt; heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(360)

&lt;400&gt; 177

gag gtc cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg	48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly	
1 5 10 15	

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt	96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser	
20 25 30	

aac tgg tgg agt tgg atc cgg cag ccc cca ggg aag ggg ctg gag tgg	144
Asn Trp Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp	
35 40 45	

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc	192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu	
50 55 60	

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc	240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser	
65 70 75 80	

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt	288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	

gcg aga gat agc agc agc tgg tac tac ggt atg gac gtc tgg ggc caa	336
Ala Arg Asp Ser Ser Ser Trp Tyr Tyr Gly Met Asp Val Trp Gly Gln	
100 105 110	

ggg acc acg gtc acc gtc tca agc	360
Gly Thr Thr Val Thr Val Ser Ser	
115 120	

&lt;210&gt; 178

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 178

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Asn Trp Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Ser Ser Ser Trp Tyr Tyr Gly Met Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> 179  
 <211> 348  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(348)

<400> 179  
 gag gtc cag ctg gtg gag tcc ggc cca gga ctg gtg aag cct tcg gag 48  
 Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60  
 aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80  
 ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gta tat tat tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga tcg acg tgg tcc ctt gac tac tgg ggc cag ggc acc ctg gtc 336  
 Ala Arg Ser Thr Trp Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val  
                   100                  105                  110

acc gtc tca agc 348  
 Thr Val Ser Ser  
                   115

<210> 180  
 <211> 116  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 180

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1                  5                  10                  15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
                   20                  25                  30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
                   35                  40                  45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
                   50                  55                  60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                   85                  90                  95

Ala Arg Ser Thr Trp Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val  
                   100                  105                  110

Thr Val Ser Ser  
                   115

<210> 181  
 <211> 354  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(354)

&lt;400&gt; 181

gag gtc cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg 48  
 Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gta tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga ctc tcg ttt gcc gat cct ttt gat atc tgg ggc caa ggg aca 336  
 Ala Arg Leu Ser Phe Ala Asp Pro Phe Asp Ile Trp Gly Gln Gly Thr  
 100 105 110

atg gtc acc gtc tca agc 354  
 Met Val Thr Val Ser Ser  
 115

&lt;210&gt; 182

&lt;211&gt; 118

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 182

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu

127

ggc aaa ggg acc acg gtc acc gtc tca agc  
 Gly Lys Gly Thr Thr Val Thr Val Ser Ser  
       115                      120

366

<210> 184  
 <211> 122  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 184

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
   1                      5                      10                      15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr  
           20                      25                      30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
       35                      40                      45

Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe  
       50                      55                      60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr  
       65                      70                      75                      80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
           85                      90                      95

Ala Tyr Gly Ser Gly Ser Tyr Tyr Asp Tyr Tyr Tyr Met Asp Val Trp  
           100                      105                      110

Gly Lys Gly Thr Thr Val Thr Val Ser Ser  
       115                      120

<210> 185  
 <211> 357  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(357)  
 <400> 185

gag gtc cag ctg gtg cag tct ggg gga ggc ttg gtc cag cct ggg ggg 48  
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

tcc ctg aga ctc tcc tgt tca gcc tcc gga ttc acc ttc agt agc tat 96  
 Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

gct atg cac tgg gtc cgc cag gct cca ggg aag gga ctg gaa tat gtt 144  
 Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val  
 35 40 45

tca act att agt agt aat ggg gat agc aca tac tac gca gac tcc gtg 192  
 Ser Thr Ile Ser Ser Asn Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60

aag ggc aga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt 288  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aaa gaa gaa gta tgg cta cag gct ttt gat atc tgg ggc caa ggg 336  
 Ala Lys Glu Glu Val Trp Leu Gln Ala Phe Asp Ile Trp Gly Gln Gly  
 100 105 110

aca atg gtc acc gtc tca agc 357  
 Thr Met Val Thr Val Ser Ser  
 115

<210> 186  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 186

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val  
 35 40 45

Ser Thr Ile Ser Ser Asn Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
                     85                    90                    95

Ala Lys Glu Glu Val Trp Leu Gln Ala Phe Asp Ile Trp Gly Gln Gly  
                     100                    105                    110

Thr Met Val Thr Val Ser Ser  
                     115

<210> 187  
 <211> 345  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(345)

<400> 187  
 cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag 48  
 Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1                    5                    10                    15

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agt agt aac 96  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Asn  
                     20                    25                    30

tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg att 144  
 Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
                     35                    40                    45

ggg gaa atc tat cat agt ggg agc acc aac tac aac ccc tcc ctc aag 192  
 Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
                     50                    55                    60

agt cga gtc acc atc tca gta gac acg tcc aag aac cag ttc tcc ctg 240  
 Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65                    70                    75                    80

aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tat tac tgt gcg 288  
 Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
                     85                    90                    95

aga gat aag gga tac atg gac gtc tgg ggc aaa ggg acc acg gtc acc 336  
 Arg Asp Lys Gly Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr  
                     100                    105                    110

gtc tca agc 345  
 Val Ser Ser  
                     115



<210> 188  
 <211> 115  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 188

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Asn  
 20 25 30

Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
 35 40 45

Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
 50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
 85 90 95

Arg Asp Lys Gly Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr  
 100 105 110

Val Ser Ser  
 115

<210> 189  
 <211> 363  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(363)

<400> 189

cag gta cag ctg cag cag tca ggg gct gag gtg aag aag cct ggg tcc 48  
 Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15

tcg gtg aag gtc tcc tgc aag gct tct gga ggc acc ttc agc agc tat 96

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr  
 20 25 30

gct atc agc tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

gga agg atc atc cct atc ctt ggt ata gca aac tac gca cag aag ttc 192  
 Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe  
 50 55 60

cag ggc aga gtc acg att acc gcg gac aaa tcc acg agc aca gcc tac 240  
 Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr  
 65 70 75 80

atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt 288  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga gat cat agg ttc gac tac gcc tgg tac ttc gat ctc tgg ggc 336  
 Ala Arg Asp His Arg Phe Asp Tyr Ala Trp Tyr Phe Asp Leu Trp Gly  
 100 105 110

cgt ggc acc ctg gtc acc gtc tca agc 363  
 Arg Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> 190  
 <211> 121  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 190

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr  
 20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp His Arg Phe Asp Tyr Ala Trp Tyr Phe Asp Leu Trp Gly  
                   100                  105                  110

Arg Gly Thr Leu Val Thr Val Ser Ser  
           115                  120

<210> 191  
 <211> 351  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(351)

<400> 191  
 cag gtg cag ctg cag gag tcg ggc cca gga ctg ctg aag cct tcg ggg 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Leu Lys Pro Ser Gly  
 1                  5                  10                  15  
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agc 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
                   20                  25                  30  
 aac tgg tgg agt tgg gtc cgc cag ccc cca ggg gag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp  
                   35                  40                  45  
 att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
 Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
                   50                  55                  60  
 aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65                  70                  75                  80  
 ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtc tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
                   85                  90                  95  
 gcg aga gat cta acg ggg agt ctt gac tac tgg ggc cag gga acc ctg 336  
 Ala Arg Asp Leu Thr Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu  
                   100                  105                  110  
 gtc acc gtc tca agc 351  
 Val Thr Val Ser Ser  
                   115

<210> 192  
 <211> 117  
 <212> PRT  
 <213> Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 192

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Leu Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Leu Thr Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu  
 100 105 110

Val Thr Val Ser Ser  
 115

&lt;210&gt; 193

&lt;211&gt; 351

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; heavy chain variable region

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(351)

&lt;400&gt; 193

cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg 48  
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp

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          35              40              45
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc etc      192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
 65              70              75              80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
    85              90              95

gcg aga ata cgc tat gat gct ttt gat atc tgg ggc caa ggg aca atg      336
Ala Arg Ile Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
    100              105              110

gtc acc gtc tca agc      351
Val Thr Val Ser Ser
    115

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<210> 194  
 <211> 117  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 194

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1              5              10              15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
    20              25              30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
    35              40              45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
 65              70              75              80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
    85              90              95

Ala Arg Ile Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
    100              105              110

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Val Thr Val Ser Ser  
115

<210> 195  
<211> 354  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(354)

<400> 195  
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
1 5 10 15  
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30  
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60  
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80  
ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tat tac tgt 288  
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcc gtg acg gca gcc cat gat gct ttt gat atc tgg ggc caa ggg aca 336  
Ala Val Thr Ala Ala His Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
100 105 110  
atg gtc acc gtc tca agc 354  
Met Val Thr Val Ser Ser  
115

<210> 196  
<211> 118  
<212> PRT  
<213> Artificial

<220>  
<223> Synthetic Construct

<400> 196

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Val Thr Ala Ala His Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr  
100 105 110

Met Val Thr Val Ser Ser  
115

<210> 197  
<211> 357  
<212> DNA  
<213> Artificial

<220>  
<223> heavy chain variable region

<220>  
<221> CDS  
<222> (1)..(357)

<400> 197  
cag gtg cag cta cag cag tgg ggc cca gga ctg gtg aag cct tcg ggg 48  
Gln Val Gln Leu Gln Gln Trp Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt 96  
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
20 25 30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg 144  
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc 192  
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc 240  
 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt 288  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga gac agc agt ggc caa ggg tac ttt gac tac tgg ggc cag ggc 336  
 Ala Arg Asp Ser Ser Gly Gln Gly Tyr Phe Asp Tyr Trp Gly Gln Gly  
 100 105 110

acc ctg gtc acc gtc tca agc 357  
 Thr Leu Val Thr Val Ser Ser  
 115

<210> 198  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 198

Gln Val Gln Leu Gln Gln Trp Gly Pro Gly Leu Val Lys Pro Ser Gly  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser  
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Ser Ser Gly Gln Gly Tyr Phe Asp Tyr Trp Gly Gln Gly  
 100 105 110

Thr Leu Val Thr Val Ser Ser  
 115

<210> 199



<211> 354  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(354)

<400> 199  
 gag gtg cag ctg gtg cag tct ggg gct gag gtg aag aag cct ggg gcc 48  
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15  
 tca gtg aag gtc tcc tgc aag gct tct gga tac acc ttc act agc tat 96  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr  
 20 25 30  
 gct atg cat tgg gtg cgc cag gcc ccc gga caa agg ctt gag tgg atg 144  
 Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met  
 35 40 45  
 gga tgg atc aac gct ggc aat ggt aac aca aaa tat tca cag aag ttc 192  
 Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Lys Phe  
 50 55 60  
 cag ggc aga gtc acc atg acc agg gac acg tcc acg agc aca gtc tac 240  
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80  
 atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt 288  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gct aga cac tcg tac tac tac ggt atg gac gtc tgg ggc caa ggc acc 336  
 Ala Arg His Ser Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr  
 100 105 110  
 ctg gtc acc gtc tca agc 354  
 Leu Val Thr Val Ser Ser  
 115

<210> 200  
 <211> 118  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 200

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30  
 Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met  
 35 40 45  
 Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Lys Phe  
 50 55 60  
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg His Ser Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr  
 100 105 110  
 Leu Val Thr Val Ser Ser  
 115

<210> 201  
 <211> 360  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(360)

<400> 201  
 cag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag 48  
 Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
 1 5 10 15  
 acc ctg tcc ctc acc tgc gct gtc tat ggt ggg tcc ttc agt ggt tac 96  
 Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr  
 20 25 30  
 tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg ctg gag tgg att 144  
 Tyr Trp Ser Trp Ile Arg Gln Pro Gly Lys Gly Leu Glu Trp Ile  
 35 40 45  
 ggg gaa atc aat cat agt gga agc acc aac tac aac ccg tcc ctc aag 192  
 Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
 50 55 60  
 agt cga gtc acc ata tcg gta gac acg tcc aag aac cag ttc tcc ctg 240  
 Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65 70 75 80

aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg 288  
 Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
                   85                                  90                                  95

aga gtc ggg tat agc cac ggc gaa gaa gtc ctg gac gtc tgg ggc aaa 336  
 Arg Val Gly Tyr Ser His Gly Glu Glu Val Leu Asp Val Trp Gly Lys  
                   100                                  105                                  110

ggg acc acg gtc acc gtc tca agc 360  
 Gly Thr Thr Val Thr Val Ser Ser  
                   115                                  120

<210> 202  
 <211> 120  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 202

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
 1                  5                                  10                                  15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr  
                   20                                  25                                  30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
                   35                                  40                                  45

Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
                   50                                  55                                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
 65                                  70                                  75                                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
                   85                                  90                                  95

Arg Val Gly Tyr Ser His Gly Glu Glu Val Leu Asp Val Trp Gly Lys  
                   100                                  105                                  110

Gly Thr Thr Val Thr Val Ser Ser  
                   115                                  120

<210> 203  
 <211> 354  
 <212> DNA  
 <213> Artificial

<220>

<223> heavy chain variable region

<220>

<221> CDS

<222> (1) .. (354)

<400> 203

cag	gtg	cag	ctg	cag	gag	tcg	ggc	cca	gga	ctg	gtg	aag	cct	tcg	gag	48
Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu	
1				5					10					15		

acc	ctg	tcc	ctc	acc	tgc	act	gtc	tct	ggg	ggc	tcc	atc	ggc	aat	tat	96
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Gly	Asn	Tyr	
			20					25					30			

gac	tgg	agt	tgg	atc	cgg	cag	ccc	cca	ggg	aag	gga	ctg	gag	tgg	att	144
Asp	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile	
		35					40					45				

ggg	act	atc	tac	tct	agt	ggg	agt	acg	tac	tac	agt	ccg	tcc	ctc	aag	192
Gly	Thr	Ile	Tyr	Ser	Ser	Gly	Ser	Thr	Tyr	Tyr	Ser	Pro	Ser	Leu	Lys	
	50					55					60					

agt	cga	ctc	acc	ata	tca	gta	gac	aag	tcc	aag	aac	cgg	ttc	tcc	ctg	240
Ser	Arg	Leu	Thr	Ile	Ser	Val	Asp	Lys	Ser	Lys	Asn	Arg	Phe	Ser	Leu	
65					70					75					80	

aag	ctg	agc	tct	gtg	acc	gcc	gcg	gac	acg	gcc	gtg	tat	tac	tgt	gcg	288
Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	
				85				90						95		

aga	gca	cga	ggg	tat	agc	agc	ccc	ttc	gac	ccc	tgg	ggc	cag	ggc	acc	336
Arg	Ala	Arg	Gly	Tyr	Ser	Ser	Pro	Phe	Asp	Pro	Trp	Gly	Gln	Gly	Thr	
			100					105					110			

ctg	gtc	acc	gtc	tca	agc											354
Leu	Val	Thr	Val	Ser	Ser											
			115													

<210> 204

<211> 118

<212> PRT

<213> Artificial

<220>

<223> Synthetic Construct

<400> 204

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5					10					15	

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Gly	Asn	Tyr
			20					25					30		

Asp	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile
		35					40					45			

Gly Thr Ile Tyr Ser Ser Gly Ser Thr Tyr Tyr Ser Pro Ser Leu Lys  
 50 55 60

Ser Arg Leu Thr Ile Ser Val Asp Lys Ser Lys Asn Arg Phe Ser Leu  
 65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
 85 90 95

Arg Ala Arg Gly Tyr Ser Ser Pro Phe Asp Pro Trp Gly Gln Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser  
 115

<210> 205  
 <211> 357  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS  
 <222> (1)..(357)

<400> 205  
 cag gtc cag ctg gta cag tct ggg gct gag gtg aag aag cct ggg tcc 48  
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15  
 tcg gtg aag gtc tcc tgc aag gct tct gga ggc acc ttc agc agc tat 96  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr  
 20 25 30  
 gct atc agc tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 gga ata atc aac cct agt ggt ggt agc aca agc tac gca cag aag ttc 192  
 Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe  
 50 55 60  
 cag ggc aga gtc acc att acc agg gac aca tcc gcg agc aca gcc tac 240  
 Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr  
 65 70 75 80  
 atg gag ctg agc agc ctg aga tct gaa gac acg gct gtg tat tac tgt 288  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga gat cgg tgg agg tac gat gct ttt gat atc tgg ggc caa ggg 336

Ala Arg Asp Arg Trp Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly  
 100 105 110

aca atg gtc acc gtc tca agc  
 Thr Met Val Thr Val Ser Ser  
 115

357

<210> 206  
 <211> 119  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 206

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr  
 20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Arg Trp Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly  
 100 105 110

Thr Met Val Thr Val Ser Ser  
 115

<210> 207  
 <211> 348  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain variable region

<220>  
 <221> CDS

&lt;222&gt; (1)..(348)

&lt;400&gt; 207

```

gag gtg cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg      48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1          5          10          15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
          20          25          30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg      144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
          35          40          45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
          50          55          60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65          70          75          80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
          85          90          95

gcg aga gaa aaa tcg ggt atg gac gtc tgg ggc caa ggg acc acg gtc      336
Ala Arg Glu Lys Ser Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
          100          105          110

acc gtc tca agc
Thr Val Ser Ser
          115

```

&lt;210&gt; 208

&lt;211&gt; 116

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Synthetic Construct

&lt;400&gt; 208

```

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1          5          10          15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
          20          25          30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
          35          40          45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
          50          55          60

```

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser  
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Glu Lys Ser Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val  
100 105 110

Thr Val Ser Ser  
115

<210> 209  
<211> 321  
<212> DNA  
<213> Artificial

<220>  
<223> light chain constant region

<220>  
<221> CDS  
<222> (1)..(321)

<400> 209  
cga act gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag 48  
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu  
1 5 10 15  
  
cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc 96  
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe  
20 25 30  
  
tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa 144  
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln  
35 40 45  
  
tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc 192  
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser  
50 55 60  
  
acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag 240  
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu  
65 70 75 80  
  
aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg 288  
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
85 90 95  
  
ccc gtc aca aag agc ttc aac agg gga gag tgt 321  
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
100 105

<210> 210



<211> 107  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 210

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu  
 1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe  
 20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln  
 35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser  
 50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu  
 65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
 85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
 100 105

<210> 211  
 <211> 990  
 <212> DNA  
 <213> Artificial

<220>  
 <223> heavy chain constant region

<220>  
 <221> CDS  
 <222> (1)..(990)

<400> 211  
 gcc tcc acc aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag 48  
 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys  
 1 5 10 15  
 agc acc tct ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac 96  
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr  
 20 25 30  
 ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc 144  
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser

35					40					45						
ggc	gtg	cac	acc	ttc	ccg	gct	gtc	cta	cag	tcc	tca	gga	ctc	tac	tcc	192
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	
	50					55					60					
ctc	agc	agc	gtg	gtg	acc	gtg	ccc	tcc	agc	agc	ttg	ggc	acc	cag	acc	240
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	
65					70					75					80	
tac	atc	tgc	aac	gtg	aat	cac	aag	ccc	agc	aac	acc	aag	gtg	gac	aag	288
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
				85					90					95		
aaa	gtt	gag	ccc	aaa	tct	tgt	gac	aaa	act	cac	aca	tgc	cca	ccg	tgc	336
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	
			100					105					110			
cca	gca	cct	gaa	ctc	ctg	ggg	gga	ccg	tca	gtc	ttc	ctc	ttc	ccc	cca	384
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	
		115				120						125				
aaa	ccc	aag	gac	acc	ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	432
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	
	130					135					140					
gtg	gtg	gtg	gac	gtg	agc	cac	gaa	gac	cct	gag	gtc	aag	ttc	aac	tgg	480
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	
145					150					155					160	
tac	gtg	gac	ggc	gtg	gag	gtg	cat	aat	gcc	aag	aca	aag	ccg	cgg	gag	528
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	
				165					170					175		
gag	cag	tac	aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	576
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	
			180					185					190			
cac	cag	gac	tgg	ctg	aat	ggc	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	624
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	
		195				200						205				
aaa	gcc	ctc	cca	gcc	ccc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	672
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	
	210					215					220					
cag	ccc	cga	gaa	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cgg	gat	gag	720
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	
225					230					235					240	
ctg	acc	aag	aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	768
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	
				245					250					255		
ccc	agc	gac	atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	816
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	
			260					265					270			
aac	tac	aag	acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	864
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	
		275					280					285				

ctc tat agc aag ctc acc gtg gac aag agc agg tgg cag cag ggg aac 912  
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn  
 290 295 300

gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac tac acg 960  
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr  
 305 310 315 320

cag aag agc ctc tcc ctg tct ccg ggt aaa 990  
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 325 330

<210> 212  
 <211> 330  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Synthetic Construct

<400> 212

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys  
 1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr  
 20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser  
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser  
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr  
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys  
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys  
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro  
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys  
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp

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145                150                155                160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                170                175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
                180                185                190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                195                200                205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                210                215                220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                230                235                240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                250                255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
                260                265                270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                275                280                285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290                295                300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                310                315                320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                330

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<210> 213
<211> 9
<212> PRT
<213> Artificial

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<220>
<223> Light chain CDR3

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<220>
<221> misc_feature
<222> (8)..(8)
<223> Xaa can be any naturally occurring amino acid

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<400> 213

Met Gln Ala Leu Gln Thr Pro Xaa Thr  
1 5

<210> 214

<211> 9

<212> PRT

<213> Artificial

<220>

<223> Light chain CDR3

<220>

<221> MISC\_FEATURE

<222> (3)..(3)

<223> x is arginine or serine

<220>

<221> MISC\_FEATURE

<222> (4)..(4)

<223> x is asparagine or serine

<220>

<221> MISC\_FEATURE

<222> (5)..(5)

<223> x is serine or asparagine

<220>

<221> MISC\_FEATURE

<222> (6)..(6)

<223> x is glycine, alanine, valine, leucine, isoleucine, proline,  
phenylalanine, methionine, tryptophan or cysteine

<400> 214

Gln Gln Xaa Xaa Xaa Xaa Pro Leu Thr  
1 5

<210> 215

<211> 10

<212> PRT

<213> Artificial

<220>

<223> Light chain CDR3

<220>

<221> MISC\_FEATURE

<222> (8)..(9)

<223> x is arginine, valine, or isoleucine or no amino acid

<400> 215

Gln Ser Tyr Asp Ser Ser Asn Xaa Xaa Val  
1 5 10

<210> 216  
<211> 8  
<212> PRT  
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<220>  
<223> Heavy chain CDR3

<220>  
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<222> (1)..(8)

<400> 216

Ser Arg Leu Asp Ala Phe Asp Ile  
1 5

<210> 217  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain CDR3

<220>  
<221> misc\_feature  
<222> (2)..(2)  
<223> Xaa can be any naturally occurring amino acid

<400> 217

Ser Xaa Tyr Asp Tyr Tyr Gly Met Asp Val  
1 5 10

<210> 218  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain CDR3

<220>  
<221> misc\_feature  
<222> (3)..(3)  
<223> Xaa can be any naturally occurring amino acid

<220>  
<221> misc\_feature  
<222> (5)..(5)  
<223> Xaa can be any naturally occurring amino acid

<400> 218

His Arg Xaa Asp Xaa Ala Trp Tyr Phe Asp Leu  
1 5 10

<210> 219  
<211> 4  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain CDR3

<220>  
<221> MISC\_FEATURE  
<222> (1)..(4)

<400> 219

Asp Ser Ser Gly  
1

<210> 220  
<211> 16  
<212> PRT  
<213> Artificial

<220>  
<223> Light chain CDR1

<220>  
<221> MISC\_FEATURE  
<222> (1)..(16)

<400> 220

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp  
1 5 10 15

<210> 221  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Light chain CDR1

<220>  
<221> MISC\_FEATURE  
<222> (5)..(5)  
<223> x is glycine or serine

<220>  
<221> MISC\_FEATURE  
<222> (6)..(6)  
<223> x is isoleucine or valine

<220>  
 <221> MISC\_FEATURE  
 <222> (7)..(7)  
 <223> x is glycine or serine

<220>  
 <221> MISC\_FEATURE  
 <222> (8)..(8)  
 <223> x is any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (9)..(9)  
 <223> x is tyrosine or phenyalanine

<220>  
 <221> MISC\_FEATURE  
 <222> (11)..(11)  
 <223> x is alanine or asparagine

<400> 221

Arg Ala Ser Gln Xaa Xaa Xaa Xaa Xaa Leu Xaa  
 1 5 10

<210> 222  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Light chain CDR1

<220>  
 <221> MISC\_FEATURE  
 <222> (6)..(6)  
 <223> Xaa is leucine or serine

<220>  
 <221> MISC\_FEATURE  
 <222> (7)..(11)  
 <223> x is independently any amino acid

<400> 222

Arg Ser Ser Gln Ser Xaa Xaa Xaa Xaa Xaa Xaa  
 1 5 10

<210> 223  
 <211> 7  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Light chain CDR2

<400> 223



Leu Gly Ser Asn Arg Ala Ser  
1 5

<210> 224  
<211> 7  
<212> PRT  
<213> Artificial

<220>  
<223> Light chain CDR2

<400> 224

Ala Ala Ser Thr Leu Gln Ser  
1 5

<210> 225  
<211> 7  
<212> PRT  
<213> Artificial

<220>  
<223> Light chain CDR2

<220>  
<221> misc\_feature  
<222> (4)..(4)  
<223> Xaa can be any naturally occurring amino acid

<400> 225

Glu Asp Asn Xaa Arg Pro Ser  
1 5

<210> 226  
<211> 6  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain CDR1

<400> 226

Ser Ser Asn Trp Trp Ser  
1 5

<210> 227  
<211> 5  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain CDR1

<220>  
<221> misc\_feature  
<222> (1)..(1)  
<223> Xaa can be any naturally occurring amino acid  
  
<400> 227

Xaa Tyr Tyr Trp Ser  
1 5

<210> 228  
<211> 5  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain CDR1

<220>  
<221> MISC\_FEATURE  
<222> (5)..(5)  
<223> x is serine or histidine  
  
<400> 228

Ser Tyr Ala Met Xaa  
1 5

<210> 229  
<211> 16  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain CDR2

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa = glutamic acid or isoleucine

<220>  
<221> MISC\_FEATURE  
<222> (2)..(2)  
<223> Xaa = isoleucine or valine

<220>  
<221> MISC\_FEATURE  
<222> (3)..(3)  
<223> Xaa = tyrosine or asparagine

<220>  
<221> MISC\_FEATURE  
<222> (4)..(4)  
<223> Xaa = histidine or tyrosine

<220>

<221> MISC\_FEATURE  
 <222> (9)..(9)  
 <223> Xaa = asparagine or tyrosine

<400> 229

Xaa	Xaa	Xaa	Xaa	Ser	Gly	Ser	Thr	Xaa	Tyr	Asn	Pro	Ser	Leu	Lys	Ser
1				5					10					15	

<210> 230  
 <211> 17  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Heavy chain CDR2

<220>  
 <221> MISC\_FEATURE  
 <222> (1)..(1)  
 <223> Xaa = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (4)..(4)  
 <223> Xaa = glycine or serine

<220>  
 <221> MISC\_FEATURE  
 <222> (7)..(7)  
 <223> Xaa = glycine or serine

<400> 230

Xaa	Ile	Ser	Xaa	Ser	Gly	Xaa	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 231  
 <211> 1162  
 <212> PRT  
 <213> Artificial

<220>  
 <223> huIGF-1R:Fc

<220>  
 <221> MISC\_FEATURE  
 <222> (1)..(1162)

<400> 231

Met	Lys	Ser	Gly	Ser	Gly	Gly	Gly	Ser	Pro	Thr	Ser	Leu	Trp	Gly	Leu
1				5					10					15	

Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile  
 20 25 30  
 Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg  
 35 40 45  
 Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile  
 50 55 60  
 Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val  
 65 70 75 80  
 Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu  
 85 90 95  
 Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe  
 100 105 110  
 Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile  
 115 120 125  
 Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu  
 130 135 140  
 Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile  
 145 150 155 160  
 Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys  
 165 170 175  
 Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys  
 180 185 190  
 Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr  
 195 200 205  
 Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys  
 210 215 220  
 Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser  
 225 230 235 240  
 Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr  
 245 250 255

Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu  
 260 265 270

Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala  
 275 280 285

Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met  
 290 295 300

Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr  
 305 310 315 320

Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys  
 325 330 335

Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly  
 340 345 350

Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn  
 355 360 365

Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val  
 370 375 380

Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser  
 385 390 395 400

Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly  
 405 410 415

Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp  
 420 425 430

Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe  
 435 440 445

Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu  
 450 455 460

Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg  
 465 470 475 480

Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr  
 485 490 495

Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr  
 500 505 510

Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys  
 515 520 525

Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys  
 530 535 540

Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys  
 545 550 555 560

Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln  
 565 570 575

Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp  
 580 585 590

His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala  
 595 600 605

Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser  
 610 615 620

Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn  
 625 630 635 640

Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr  
 645 650 655

Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys  
 660 665 670

Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys  
 675 680 685

Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys  
 690 695 700

Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys  
 705 710 715 720

Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu  
 725 730 735

Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser

161

Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu  
 995 1000 1005

Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile  
 1010 1015 1020

Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val  
 1025 1030 1035

Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys  
 1040 1045 1050

Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro  
 1055 1060 1065

Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met  
 1070 1075 1080

Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp  
 1085 1090 1095

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met  
 1100 1105 1110

Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln  
 1115 1120 1125

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu  
 1130 1135 1140

His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His  
 1145 1150 1155

Ser Pro Gly Lys  
 1160

<210> 232  
 <211> 1180  
 <212> PRT  
 <213> Artificial

<220>  
 <223> hu INSR:fc

<220>  
 <221> MISC\_FEATURE



&lt;222&gt; (1) .. (1180)

&lt;400&gt; 232

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Met Gly Thr Gly Gly Arg Arg Gly Ala Ala Ala Ala Pro Leu Leu Val
1          5          10          15

Ala Val Ala Ala Leu Leu Leu Gly Ala Ala Gly His Leu Tyr Pro Gly
20          25          30

Glu Val Cys Pro Gly Met Asp Ile Arg Asn Asn Leu Thr Arg Leu His
35          40          45

Glu Leu Glu Asn Cys Ser Val Ile Glu Gly His Leu Gln Ile Leu Leu
50          55          60

Met Phe Lys Thr Arg Pro Glu Asp Phe Arg Asp Leu Ser Phe Pro Lys
65          70          75          80

Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu Phe Arg Val Tyr Gly Leu
85          90          95

Glu Ser Leu Lys Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Ser
100         105         110

Arg Leu Phe Phe Asn Tyr Ala Leu Val Ile Phe Glu Met Val His Leu
115         120         125

Lys Glu Leu Gly Leu Tyr Asn Leu Met Asn Ile Thr Arg Gly Ser Val
130         135         140

Arg Ile Glu Lys Asn Asn Glu Leu Cys Tyr Leu Ala Thr Ile Asp Trp
145         150         155         160

Ser Arg Ile Leu Asp Ser Val Glu Asp Asn His Ile Val Leu Asn Lys
165         170         175

Asp Asp Asn Glu Glu Cys Gly Asp Ile Cys Pro Gly Thr Ala Lys Gly
180         185         190

Lys Thr Asn Cys Pro Ala Thr Val Ile Asn Gly Gln Phe Val Glu Arg
195         200         205

Cys Trp Thr His Ser His Cys Gln Lys Val Cys Pro Thr Ile Cys Lys
210         215         220

Ser His Gly Cys Thr Ala Glu Gly Leu Cys Cys His Ser Glu Cys Leu

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225		230		235		240
Gly Asn Cys Ser	Gln Pro Asp Asp Pro Thr Lys Cys Val	Ala Cys Arg				
	245		250		255	
Asn Phe Tyr Leu	Asp Gly Arg Cys Val Glu Thr Cys Pro	Pro Pro Tyr				
	260		265		270	
Tyr His Phe Gln	Asp Trp Arg Cys Val Asn Phe Ser	Phe Cys Gln Asp				
	275		280		285	
Leu His His Lys	Cys Lys Asn Ser Arg Arg Gln Gly Cys	His Gln Tyr				
	290		295		300	
Val Ile His Asn	Asn Lys Cys Ile Pro Glu Cys Pro Ser Gly Tyr	Thr				
305		310		315		320
Met Asn Ser Ser	Asn Leu Leu Cys Thr Pro Cys Leu Gly	Pro Cys Pro				
	325		330		335	
Lys Val Cys His	Leu Leu Glu Gly Glu Lys Thr Ile Asp	Ser Val Thr				
	340		345		350	
Ser Ala Gln Glu	Leu Arg Gly Cys Thr Val Ile Asn Gly	Ser Leu Ile				
	355		360		365	
Ile Asn Ile Arg	Gly Gly Asn Asn Leu Ala Ala Glu Leu Glu	Ala Asn				
	370		375		380	
Leu Gly Leu Ile	Glu Glu Ile Ser Gly Tyr Leu Lys Ile Arg	Arg Ser				
385		390		395		400
Tyr Ala Leu Val	Ser Leu Ser Phe Phe Arg Lys Leu Arg	Leu Ile Arg				
	405		410		415	
Gly Glu Thr Leu	Glu Ile Gly Asn Tyr Ser Phe Tyr Ala	Leu Asp Asn				
	420		425		430	
Gln Asn Leu Arg	Gln Leu Trp Asp Trp Ser Lys His Asn	Leu Thr Thr				
	435		440		445	
Thr Gln Gly Lys	Leu Phe Phe His Tyr Asn Pro Lys Leu Cys	Leu Ser				
	450		455		460	
Glu Ile His Lys	Met Glu Glu Val Ser Gly Thr Lys Gly Arg	Gln Glu				
465		470		475		480

Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Lys Ala Ser Cys Glu  
 485 490 495

Asn Glu Leu Leu Lys Phe Ser Tyr Ile Arg Thr Ser Phe Asp Lys Ile  
 500 505 510

Leu Leu Arg Trp Glu Pro Tyr Trp Pro Pro Asp Phe Arg Asp Leu Leu  
 515 520 525

Gly Phe Met Leu Phe Tyr Lys Glu Ala Pro Tyr Gln Asn Val Thr Glu  
 530 535 540

Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser Trp Thr Val Val Asp  
 545 550 555 560

Ile Asp Pro Pro Leu Arg Ser Asn Asp Pro Lys Ser Gln Asn His Pro  
 565 570 575

Gly Trp Leu Met Arg Gly Leu Lys Pro Trp Thr Gln Tyr Ala Ile Phe  
 580 585 590

Val Lys Thr Leu Val Thr Phe Ser Asp Glu Arg Arg Thr Tyr Gly Ala  
 595 600 605

Lys Ser Asp Ile Ile Tyr Val Gln Thr Asp Ala Thr Asn Pro Ser Val  
 610 615 620

Pro Leu Asp Pro Ile Ser Val Ser Asn Ser Ser Ser Gln Ile Ile Leu  
 625 630 635 640

Lys Trp Lys Pro Pro Ser Asp Pro Asn Gly Asn Ile Thr His Tyr Leu  
 645 650 655

Val Phe Trp Glu Arg Gln Ala Glu Asp Ser Glu Leu Phe Glu Leu Asp  
 660 665 670

Tyr Cys Leu Lys Gly Leu Lys Leu Pro Ser Arg Thr Trp Ser Pro Pro  
 675 680 685

Phe Glu Ser Glu Asp Ser Gln Lys His Asn Gln Ser Glu Tyr Glu Asp  
 690 695 700

Ser Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp Ser Gln Ile Leu  
 705 710 715 720

Lys Glu Leu Glu Glu Ser Ser Phe Arg Lys Thr Phe Glu Asp Tyr Leu  
                     725                    730                    735

His Asn Val Val Phe Val Pro Arg Lys Thr Ser Ser Gly Thr Gly Ala  
                     740                    745                    750

Glu Asp Pro Arg Pro Ser Arg Lys Arg Arg Ser Leu Gly Asp Val Gly  
                     755                    760                    765

Asn Val Thr Val Ala Val Pro Thr Val Ala Ala Phe Pro Asn Thr Ser  
                     770                    775                    780

Ser Thr Ser Val Pro Thr Ser Pro Glu Glu His Arg Pro Phe Glu Lys  
 785                    790                    795                    800

Val Val Asn Lys Glu Ser Leu Val Ile Ser Gly Leu Arg His Phe Thr  
                     805                    810                    815

Gly Tyr Arg Ile Glu Leu Gln Ala Cys Asn Gln Asp Thr Pro Glu Glu  
                     820                    825                    830

Arg Cys Ser Val Ala Ala Tyr Val Ser Ala Arg Thr Met Pro Glu Ala  
                     835                    840                    845

Lys Ala Asp Asp Ile Val Gly Pro Val Thr His Glu Ile Phe Glu Asn  
                     850                    855                    860

Asn Val Val His Leu Met Trp Gln Glu Pro Lys Glu Pro Asn Gly Leu  
 865                    870                    875                    880

Ile Val Leu Tyr Glu Val Ser Tyr Arg Arg Tyr Gly Asp Glu Glu Leu  
                     885                    890                    895

His Leu Cys Val Ser Arg Lys His Phe Ala Leu Glu Arg Gly Cys Arg  
                     900                    905                    910

Leu Arg Gly Leu Ser Pro Gly Asn Tyr Ser Val Arg Ile Arg Ala Thr  
                     915                    920                    925

Ser Leu Ala Gly Asn Gly Ser Trp Thr Glu Pro Thr Tyr Phe Tyr Val  
                     930                    935                    940

Thr Asp Tyr Leu Asp Val Pro Ser Asn Ile Ala Lys Val Asp Gly Cys  
 945                    950                    955                    960

Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe  
                     965                                    970                                    975

Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val  
                     980                                    985                                    990

Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe  
                     995                                    1000                                    1005

Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln  
                     1010                                    1015                                    1020

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu  
                     1025                                    1030                                    1035

Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys  
                     1040                                    1045                                    1050

Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr  
                     1055                                    1060                                    1065

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr  
                     1070                                    1075                                    1080

Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu  
                     1085                                    1090                                    1095

Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu  
                     1100                                    1105                                    1110

Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln  
                     1115                                    1120                                    1125

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu  
                     1130                                    1135                                    1140

Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys  
                     1145                                    1150                                    1155

Ser Val Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser  
                     1160                                    1165                                    1170

Leu Ser His Ser Pro Gly Lys  
                     1175                                    1180

&lt;210&gt; 233

<211> 1062  
 <212> PRT  
 <213> Artificial

<220>  
 <223> hu IGF-1R:avidin

<400> 233

Met Lys Ser Gly Ser Gly Gly Gly Ser Pro Thr Ser Leu Trp Gly Leu  
 1 5 10 15

Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile  
 20 25 30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg  
 35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile  
 50 55 60

Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val  
 65 70 75 80

Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu  
 85 90 95

Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe  
 100 105 110

Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile  
 115 120 125

Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu  
 130 135 140

Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile  
 145 150 155 160

Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys  
 165 170 175

Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys  
 180 185 190

Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr  
 195 200 205

Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys  
 210 215 220  
 Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser  
 225 230 235 240  
 Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr  
 245 250 255  
 Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu  
 260 265 270  
 Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala  
 275 280 285  
 Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met  
 290 295 300  
 Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr  
 305 310 315 320  
 Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys  
 325 330 335  
 Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly  
 340 345 350  
 Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn  
 355 360 365  
 Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val  
 370 375 380  
 Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser  
 385 390 395 400  
 Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly  
 405 410 415  
 Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp  
 420 425 430  
 Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe  
 435 440 445  
 Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu

450		455		460													
Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg																	
465					470					475							480
Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr					485					490							495
Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr					500				505							510	
Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys					515				520							525	
Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys					530				535							540	
Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys					545				550							555	560
Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln					565				570								575
Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp					580				585							590	
His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala					595				600							605	
Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser					610				615							620	
Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn					625				630							635	640
Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr					645				650								655
Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys					660				665								670
Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys					675				680								685
Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys					690				695								700



Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys  
 705 710 715 720  
 Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu  
 725 730 735  
 Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser  
 740 745 750  
 Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro  
 755 760 765  
 Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn  
 770 775 780  
 Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg  
 785 790 795 800  
 Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser  
 805 810 815  
 Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp  
 820 825 830  
 Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile  
 835 840 845  
 Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met  
 850 855 860  
 Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val  
 865 870 875 880  
 Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu  
 885 890 895  
 Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly  
 900 905 910  
 Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr  
 915 920 925  
 Gly Tyr Glu Ala Ala Ala Ala Arg Lys Cys Ser Leu Thr Gly Lys Trp  
 930 935 940

Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn Ser Lys  
 945 950 955 960

Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr Ser Asn  
 965 970 975

Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile Asn Lys  
 980 985 990

Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe Ser Glu  
 995 1000 1005

Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn Gly  
 1010 1015 1020

Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn  
 1025 1030 1035

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile  
 1040 1045 1050

Phe Thr Arg Leu Arg Thr Gln Lys Glu  
 1055 1060

<210> 234  
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 <212> PRT  
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<400> 234

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu  
 1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe  
 20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln  
 35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser  
 50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu  
 65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser

85

90

95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
 100 105

<210> 235  
 <211> 330  
 <212> PRT  
 <213> Artificial

<220>  
 <223> heavy chain constant region

<400> 235

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys  
 1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr  
 20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser  
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser  
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr  
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys  
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys  
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro  
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys  
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp  
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu  
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu  
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn  
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly  
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu  
 225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr  
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn  
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe  
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn  
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr  
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 325 330

<210> 236

<211> 16

<212> PRT

<213> Artificial

<220>

<223> light chain CDR1

<220>

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<222> (9)..(9)

<223> x is serine or threonine residue

<220>

<221> MISC\_FEATURE

<222> (10)..(10)

<223> x is asparagine, serine or histidine residue

<220>

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<222> (14)..(14)  
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<220>  
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<222> (16)..(16)  
<223> x is aspartate or asparagine residue

<400> 236

Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Xaa	Xaa	Gly	Tyr	Asn	Xaa	Leu	Xaa
1				5				10						15	

<210> 237  
<211> 13  
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<220>  
<223> light chain CDR1

<220>  
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<222> (6)..(6)  
<223> x is serine or aspartate residue

<220>  
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<222> (8)..(8)  
<223> x is alanine or aspartate residue

<220>  
<221> MISC\_FEATURE  
<222> (9)..(9)  
<223> x is serine or asparagine residue

<400> 237

Thr	Arg	Ser	Ser	Gly	Xaa	Ile	Xaa	Xaa	Asn	Tyr	Val	Gln
1				5					10			

<210> 238  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR1

<220>  
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<222> (5)..(5)  
<223> x is glycine or serine residue

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<222> (6)..(6)

<223> x is isoleucine, valine or proline residue

<220>

<221> MISC\_FEATURE

<222> (7)..(7)

<223> x is serine, glycine or tyrosine residue

<220>

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<222> (8)..(8)

<223> x is any amino acid

<220>

<221> MISC\_FEATURE

<222> (9)..(9)

<223> x is phenylalanine, tyrosine, asparagine or tryptophan residue

<220>

<221> MISC\_FEATURE

<222> (11)..(11)

<223> x is alanine or asparagine residue

<400> 238

Arg	Ala	Ser	Gln	Xaa	Xaa	Xaa	Xaa	Xaa	Leu	Xaa
1				5					10	

<210> 239

<211> 7

<212> PRT

<213> Artificial

<220>

<223> light chain CDR2

<220>

<221> MISC\_FEATURE

<222> (2)..(2)

<223> x is glycine or valine residue

<220>

<221> MISC\_FEATURE

<222> (3)..(3)

<223> x is serine or phenylalanine residue

<220>

<221> MISC\_FEATURE

<222> (4)..(4)

<223> x is asparagine, tyrosine or threonine residue

<220>

<221> MISC\_FEATURE

<222> (6)..(6)

<223> x is alanine or aspartate residue

<400> 239

Leu	Xaa	Xaa	Xaa	Arg	Xaa	Ser
1				5		

<210> 240  
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<213> Artificial

<220>  
<223> light chain CDR2

<220>  
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<220>  
<221> MISC\_FEATURE  
<222> (4)..(4)  
<223> x is threonine or glycine residue

<220>  
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<222> (6)..(6)  
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<400> 240

Ala Xaa Ser Xaa Leu Xaa Ser  
1 5

<210> 241  
<211> 7  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR2

<220>  
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<220>  
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<223> x is aspartate or lysine residue

<220>  
<221> MISC\_FEATURE  
<222> (4)..(4)  
<223> x is any amino acid residue

<400> 241

Xaa Xaa Asn Xaa Arg Pro Ser  
1 5

<210> 242  
 <211> 9  
 <212> PRT  
 <213> Artificial

<220>  
 <223> light chain CDR3

<220>  
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 <222> (2)..(2)  
 <223> x is glutamine or glutamate residue

<220>  
 <221> MISC\_FEATURE  
 <222> (3)..(3)  
 <223> x is alanine, glycine, serine or threonine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (4)..(4)  
 <223> x is leucine or threonine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (5)..(5)  
 <223> x is glutamine, glutamate or histidine residue

<220>  
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 <222> (6)..(6)  
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<220>  
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 <222> (8)..(8)  
 <223> x is nonpolar side chain

<220>  
 <221> MISC\_FEATURE  
 <222> (9)..(9)  
 <223> x is threonine, serine or alanine residue

<400> 242

Met Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa  
 1 5

<210> 243  
 <211> 9  
 <212> PRT  
 <213> Artificial

<220>  
 <223> light chain CDR3

<220>



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<220>  
<221> MISC\_FEATURE  
<222> (4)..(4)  
<223> x is asparagine, serine or histidine residue

<220>  
<221> MISC\_FEATURE  
<222> (5)..(5)  
<223> x is serine or asparagine residue

<220>  
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<222> (6)..(6)  
<223> x is nonpolar side chain

<220>  
<221> MISC\_FEATURE  
<222> (8)..(8)  
<223> x is leucine, isoleucine, tyrosine or tryptophan residue

<400> 243

Gln Gln Xaa Xaa Xaa Xaa Pro Xaa Thr  
1 5

<210> 244  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
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<220>  
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<220>  
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<223> x is glutamine, valine or tryptophan residue

<220>  
<221> MISC\_FEATURE  
<222> (9)..(9)  
<223> x is arginine residue or no residue

<400> 244

Gln Ser Tyr Xaa Ser Xaa Asn Xaa Xaa Val  
1 5 10

<210> 245  
<211> 6  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR1

<220>  
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<223> serine residue or no residue

<220>  
<221> MISC\_FEATURE  
<222> (2)..(2)  
<223> x is serine or asparagine residue

<220>  
<221> MISC\_FEATURE  
<222> (3)..(3)  
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<400> 245

Xaa Xaa Xaa Trp Trp Ser  
1 5

<210> 246  
<211> 5  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR1

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<220>  
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<400> 246

Xaa Xaa Tyr Trp Ser  
1 5

<210> 247  
<211> 5

<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR1

<220>  
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<220>  
<221> MISC\_FEATURE  
<222> (4)..(4)  
<223> x is methionine or isoleucine residue

<220>  
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<222> (5)..(5)  
<223> x is serine or histidine residue

<400> 247

Ser Tyr Xaa Xaa Xaa  
1 5

<210> 248  
<211> 16  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR2

<220>  
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<223> x is glutamate, tyrosine or serine residue

<220>  
<221> MISC\_FEATURE  
<222> (2)..(2)  
<223> x is isoleucine or valine residue

<220>  
<221> MISC\_FEATURE  
<222> (3)..(3)  
<223> x is tyrosine, asparagine or serine residue

<220>  
<221> MISC\_FEATURE  
<222> (4)..(4)  
<223> x is histidine, tryosine, aspartate, or proline residue

<220>  
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<222> (5)..(5)  
<223> x is serine or arginine residue

<220>  
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 <222> (7)..(7)  
 <223> x is serine or arginine residue

<220>  
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 <222> (9)..(9)  
 <223> x is asparagine or tyrosine residue

<220>  
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 <222> (15)..(15)  
 <223> x is lysine or glutamate residue

<400> 248

Xaa	Xaa	Xaa	Xaa	Xaa	Gly	Xaa	Thr	Xaa	Tyr	Asn	Pro	Ser	Leu	Xaa	Ser
1				5					10					15	

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 <213> Artificial

<220>  
 <223> heavy chain CDR2

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 <223> x is glycine, serine or tyrosine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (5)..(5)  
 <223> x is serine, asparagine or aspartate residue

<220>  
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 <222> (6)..(6)  
 <223> x is glycine or serine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (7)..(7)  
 <223> x is glycine, serine or aspartate residue

<220>  
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 <222> (8)..(8)  
 <223> x is serine, threonine or asparagine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (9)..(9)  
 <223> x is threonine, lysine or isoleucine residue

<400> 249

Xaa	Ile	Ser	Xaa	Xaa	Xaa	Xaa	Xaa	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1			5					10					15	

Gly

<210> 250  
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 <212> PRT  
 <213> Artificial

<220>  
 <223> heavy chain CDR3

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 <223> x is glutamate or no residue

<220>  
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 <222> (2)..(2)  
 <223> x is tyrosine, glycine or serine or no residue

<220>  
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 <222> (3)..(3)  
 <223> x is serine, asparagine, tryptophan or glutamate or no residue

<220>  
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 <223> x is serine, aspartate, tryptophan, alanine, arginine, threonine, glutamine, leucine or glutamate or no residue

<220>  
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<220>  
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 <223> x is arginine, glutamine, tyosine, valine, alanine, glycine, serine, phenylalanine or tryptophan residue

<220>  
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tyrosine, valine, alanine, or histidine residue

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<220>  
 <221> MISC\_FEATURE  
 <222> (9)..(9)  
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<400> 250

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe Asp Ile  
 1 5 10

<210> 251  
 <211> 14  
 <212> PRT  
 <213> Artificial

<220>  
 <223> heavy chain CDR3

<220>  
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 <222> (1)..(1)  
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 <221> MISC\_FEATURE  
 <222> (2)..(2)  
 <223> x is glutamate, tryosine or glycine or no residue

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 <222> (3)..(3)  
 <223> x is serine, asparagine, tryptophan, glutamate or no residue

<220>  
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 <222> (4)..(4)  
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<220>  
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 <222> (5)..(5)  
 <223> x is serine, glycine, or aspartate residue, or no residue

<220>  
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 <222> (6)..(6)  
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<220>  
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<223> x i is a tyrosine, tryptophan, serine, or aspartate residue, or no residue

<220>

<221> MISC\_FEATURE

<222> (8)..(8)

<223> x is aspartate, arginine, serine, glycine, tyrosine, or tryptophan residue

<220>

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<222> (9)..(9)

<223> x is tyrosine, isoleucine, leucine, phenylalanine, or lysine residue

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<221> MISC\_FEATURE

<222> (10)..(10)

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<220>

<221> MISC\_FEATURE

<222> (11)..(11)

<223> x is glycine, tyrosine, or asparagine residue

<400> 251

Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Met	Asp	Val
1				5						10				

<210> 252

<211> 11

<212> PRT

<213> Artificial

<220>

<223> heavy chain CDR3

<220>

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<220>

<221> MISC\_FEATURE

<222> (2)..(2)

<223> x is glycine, tyrosine, arginine, or aspartate residue, or no residue,

<220>

<221> MISC\_FEATURE

<222> (3)..(3)

<223> x is asparagine, leucine, glycine, isoleucine, serine, valine, phenylalanine, or tyrosine residue, or no residue

<220>

<221> MISC\_FEATURE

<222> (4)..(4)

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glycine, or aspartate residue, or no residue

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<220>
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<222> (5)..(5)
<223> x is glycine, alanine, tyrosine, serine, aspartate, or leucine
      residue

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> x is valine, alanine, glycine, threonine, proline, histidine, or
      glutamine residue

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> x is glutamate, glycine, serine, aspartate, glycine, valine,
      tryptophan, histidine, or arginine residue

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> x is glutamine, alanine, glycine, tyrosine, proline, leucine,
      aspartate, or serine residue

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> x is nonpolar side chain residue

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> x is aspartate or alanine residue

<400> 252

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr
1              5              10

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<210> 253
<211> 14
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<213> Artificial

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<220>
<223> Heavy chain CDR3

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<220>
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<220>
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<222> (2)..(2)
<223> x is proline residue, or no residue

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<220>  
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 <222> (3)..(3)  
 <223> x is arginine or aspartate residue, or no residue

<220>  
 <221> MISC\_FEATURE  
 <222> (4)..(4)  
 <223> x is histidine or proline residue

<220>  
 <221> MISC\_FEATURE  
 <222> (5)..(5)  
 <223> x is arginine or glycine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (6)..(6)  
 <223> x is arginine, serine, or phenylalanine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (7)..(7)  
 <223> x is aspartate or serine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (8)..(8)  
 <223> x is glycine, tryptophan, or tyrosine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (9)..(9)  
 <223> x is tyrosine or alanine residue

<220>  
 <221> MISC\_FEATURE  
 <222> (10)..(10)  
 <223> x is asparagine or tryptophan residue

<220>  
 <221> MISC\_FEATURE  
 <222> (14)..(14)  
 <223> x is asparagine or leucine residue

<400> 253

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Phe Asp Xaa  
 1 5 10

<210> 254  
 <211> 15  
 <212> PRT  
 <213> Artificial

<220>  
 <223> heavy chain CDR3

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<220>  
<221> MISC\_FEATURE  
<222> (2)..(2)  
<223> x is asparagine or glycine residue, or no residue

<220>  
<221> MISC\_FEATURE  
<222> (3)..(3)  
<223> x is tyrosine or a leucine residue, or no residue

<220>  
<221> MISC\_FEATURE  
<222> (4)..(4)  
<223> x is a tyrosine or glycine residue, or no residue

<220>  
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<222> (8)..(8)  
<223> x is a glycine, serine, or valine residue

<220>  
<221> MISC\_FEATURE  
<222> (9)..(9)  
<223> x is tyrosine, phenylalanine, tryptophan, or glutamine residue,  
or no residue

<220>  
<221> MISC\_FEATURE  
<222> (10)..(10)  
<223> x is tyrosine, glycine, or isoleucine residue, or no residue

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<222> (12)..(12)  
<223> x is methionine, glycine, or phenylalanine residue, or no  
residue

<220>  
<221> MISC\_FEATURE  
<222> (13)..(13)  
<223> x is aspartate or methionine residue, or no residue

<220>  
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<222> (14)..(14)  
<223> x is a valine, aspartate, or tyrosine residue, or no residue

<220>  
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<222> (15)..(15)  
<223> x is a valine residue, or no residue

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&lt;211&gt; 8

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&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; polypeptide

&lt;400&gt; 255

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8

&lt;210&gt; 256

&lt;211&gt; 37

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; nucleic acid

&lt;400&gt; 256

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37

&lt;210&gt; 257

&lt;211&gt; 36

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&lt;223&gt; nucleic acid

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36

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&lt;211&gt; 3486

&lt;212&gt; DNA

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; nucleic acid

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